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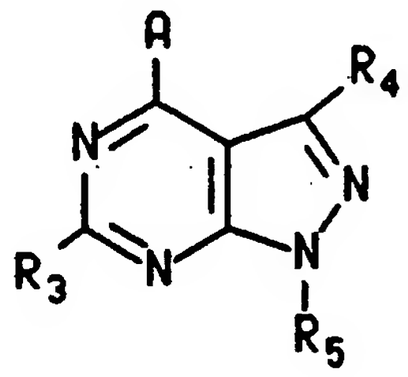

(I)

(57) Abstract

Corticotropin-releasing factor (CRF) antagonists have formula (I), wherein A, R_3, R_4 and R_5 are as defined herein. They are useful in the treatment of illnesses induced or facilitated by CRF, such as inflammatory disorders, and depression and anxiety related disorders.

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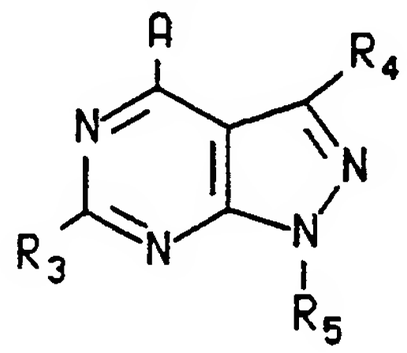
PYRAZOLOPYRIMIDINES AS CRF ANTAGONISTS

This invention relates to pyrazolopyrimidines, pharmaceutical compositions containing them, and their use in the treatment of stress-related and other diseases. The compounds have corticotropin-releasing factor (CRF) antagonist activity.

CRF antagonists are mentioned in U.S. Patents 4,605,642 and 5,063,245 referring to peptides and pyrazolinones, respectively. The importance of CRF antagonists is set out in the literature, e. g. as discussed in U.S. Patent 5,063,245, which is incorporated herein by reference. A recent outline of the different activities possessed by CRF antagonists is found in M. J. Owens et al., Pharm. Rev., Vol. 43, pages 425 to 473 (1991), also incorporated herein by reference. Based on the research described in these two and other references, CRF antagonists are considered effective in the treatment of a wide range of diseases including stress-related illnesses, such as stress-induced depression, anxiety, and headache; abdominal bowel syndrome; inflammatory diseases; immune suppression; Alzheimer's disease; gastrointestinal diseases; anorexia nervosa; hemorrhagic stress; drug and alcohol withdrawal symptoms; drug addiction, and fertility problems.

Certain substituted pyrazolopyrimidines have been described in the past. For instance, European Patent Publication 496,617 refers to adenosine kinase inhibitors among which are 1-ribofuranosylpyrazolopyrimidines and 1-(substituted ribofuranosyl)pyrazolopyrimidines. U.S. Patent No. 4,904,666 refers to pyrazolopyrimidines having 1-tetrahydrofuranyl or 1-tetrahydropyranyl substituents. Senga et at, J. Heterocyclic Chem., 19,1565 (1982) refers to certain pyrazolopyrimidines having xanthine oxidase inhibitory activity. Other pyrazolopyrimidines are mentioned in U.S. Patent Nos. 2,965,643 and 3,600,389.

The present invention relates to a pyrazolopyrimidine compound of the formula



I

and the pharmaceutically acceptable acid addition salts thereof, wherein

A is NR_1R_2, $CR_1R_2R_{11}$, $C(=CR_2R_{12})R_1$, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$ or $C(O)R_2$;

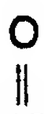
R_1 is hydrogen, or C_1-C_6 alkyl which may contain one or two double or triple bonds or which may be substituted by one or two substituents R_6 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, O-C-(C_1-C_6 alkyl), O-C-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), NH(C_1-C_4 alkyl), amino, N(C_1-C_2 alkyl) (C_1-C_4 alkyl), S(C_1-C_6 alkyl), OC-NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)C(C_1-C_4 alkyl), NHC(C_1-C_4 alkyl), COOH, CO(C_1-C_4 alkyl), CNH(C_1-C_4 alkyl), CN(C_1-C_4 alkyl)(C_1-C_2 alkyl), SO_2(C_1-C_4 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), wherein said (C_1-C_6) alkyl may have one or two double or triple bonds;

R_2 is C_1-C_{12} alkyl, aryl or (C_1-C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene) cycloalkyl, wherein said cycloalkyl may have one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl, or C_1-C_4 alkanoyl, wherein each one of the above groups may be substituted independently by from one to three of chloro, fluoro, or (C_1-C_4)alkyl, or one of hydroxy, bromo, iodo, C_1-C_6 alkoxy, O-C-(C_1-C_6 alkyl), O-C-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_6 alkyl), NH_2, NH(C_1-C_2 alkyl), N(C_1-C_2 alkyl) (C_1-C_4 alkyl), N(C_1-C_4 alkyl)C(C_1-C_4 alkyl), NHC(C_1-C_4 alkyl), COOH, CO(C_1-C_4 alkyl), CNH(C_1-C_4 alkyl), CN(C_1-C_4 alkyl)(C_1-C_2

alkyl), SH, CN, NO_2, $SO(C_1\text{-}C_4$ alkyl), $SO_2(C_1\text{-}C_4$ alkyl), $SO_2NH(C_1\text{-}C_4$ alkyl), $SO_2N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), and wherein said $C_1\text{-}C_{12}$ alkyl or $C_1\text{-}C_{10}$ alkylene may have one to three double or triple bonds; or

NR_2R_2 or $CR_1R_2R_{11}$ may form a saturated 4- to 8-membered ring optionally having one or two of O, S or N-Z wherein Z is hydrogen, $C_1\text{-}C_4$ alkyl, benzyl or $C_1\text{-}C_4$ alkanoyl;

R_3 is hydrogen, $C_1\text{-}C_6$ alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, $O(C_1\text{-}C_6$ alkyl), $NH(C_1\text{-}C_6$ alkyl), $N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), SH, $S(C_1\text{-}C_4$ alkyl), $SO(C_1\text{-}C_4$ alkyl), or $SO_2(C_1\text{-}C_4$ alkyl), wherein said $C_1\text{-}C_4$ alkyl and $C_1\text{-}C_6$ alkyl may have one or two double or triple bonds and may be substituted by from 1 to 3 substituents R_7 independently selected from the group consisting of hydroxy, amino, $C_1\text{-}C_3$ alkoxy,



dimethylamino, diethylamino, methylamino, ethylamino, $NHCCH_3$, fluoro, chloro or $C_1\text{-}C_3$ thioalkyl;

R_4 is hydrogen, $C_1\text{-}C_6$ alkyl, fluoro, chloro, bromo, iodo, $C_1\text{-}C_6$ alkoxy, amino, $NH(C_1\text{-}C_6$ alkyl), $N(C_1\text{-}C_6$ alkyl) $(C_1\text{-}C_2$ alkyl), $SO_n(C_1\text{-}C_6$ alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said $C_1\text{-}C_6$ alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido, $NHC(C_1\text{-}C_4$ alkyl), $NH(C_1\text{-}C_4$ alkyl),

$N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), $CO(C_1\text{-}C_4$ alkyl), $C_1\text{-}C_3$ alkoxy, $C_1\text{-}C_3$ thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, piperazinyl, piperidinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally having one or two of O, S or N-Z wherein Z is hydrogen, $C_1\text{-}C_4$ alkyl, $C_1\text{-}C_4$ alkanoyl, phenyl or benzyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, formyl, $C_1\text{-}C_6$ alkyl, $C_1\text{-}C_6$ alkoxy, or trifluoromethyl, or one of hydroxy, iodo, cyano, nitro, amino, cyclopropyl, $NH(C_1\text{-}C_4$ alkyl), $N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), $COO(C_1\text{-}C_4$ alkyl),

$CO(C_1\text{-}C_4$ alkyl), $SO_2NH(C_1\text{-}C_4$ alkyl), $SO_2N(C_1\text{-}C_4$ alkyl)$(C_1\text{-}C_2$ alkyl), SO_2NH_2, $NHSO_2(C_1\text{-}C_4$ alkyl), $S(C_1\text{-}C_6$ alkyl), $SO_2(C_1\text{-}C_6$ alkyl), wherein said $C_1\text{-}C_4$ alkyl and $C_1\text{-}C_6$ alkyl may have one double or triple bond and may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that R_5 is not unsubstituted phenyl;

R_{11} is hydrogen, hydroxy, fluoro, chloro, $COO(C_1\text{-}C_2$ alkyl), cyano, or $CO(C_1\text{-}C_2$ alkyl; and

R_{12} is hydrogen or $C_1\text{-}C_5$ alkyl; with the following provisos:

(a) A is not straight chain $C_1\text{-}C_{12}$ alkyl;

(b) R_5 is not a sugar group;

(c) when R_3 and R_4 are hydrogen and R_5 is chlorophenyl, then A is not $NH\text{-}CH(CH_3)\text{-}(CH_2)_3\text{-}N(C_2H_5)_2$;

(d) when R_3 and R_4 are hydrogen and A is NR_1R_2 wherein R_1 is $C_3\text{-}C_7$ cycloalkyl, and R_2 is $C_2\text{-}C_6$ alkenyl, phenyl-$(C_1\text{-}C_6$ alkylene) or hetero-$(C_1\text{-}C_6$ alkylene) wherein the hetero radical is furyl, thienyl or pyridinyl, and wherein said phenyl may be substituted by fluoro, chloro, bromo or iodo, then R_5 is not tetrahydrofuranyl or tetrahydropyranyl;

(e) when R_3 is methoxy, methylthio, or methylsulfonyl, R_4 is hydrogen, and R_5 is tetrahydrofuranyl or tetrahydropyranyl, then A is not $NH(C_1\text{-}C_2$alkyl), morpholinyl, hydrazino, or $NHC_2H_4C_6H_5$ the phenyl of which may be substituted by one methyl or two methoxy;

(f) when R_3 is hydrogen, $C_1\text{-}C_6$ alkyl, hydrazino, chloro, bromo, SH, or $S(C_1\text{-}C_4$ alkyl), R_4 is hydrogen and R_5 is $C_3\text{-}C_8$ cycloalkyl, then A is not hydrazino, $NH(C_1\text{-}C_2$ alkyl) or $N(C_1\text{-}C_6$ alkyl) $(C_1\text{-}C_{12}$ alkyl);

(g) when R_3 and R_4 are hydrogen and A is $NH(CH_2)_m$ COOH wherein m is 1-12, then R_5 is not phenyl substituted by one of fluoro, chloro, bromo or iodo;

(h) when R_3 is hydrogen, hydroxy, methylthio, chloro or NHbenzyl, R_4 is hydrogen, and R_5 is chlorophenyl or bromophenyl, then A is not $NH(C_1\text{-}C_{12}$ alkyl), NHallyl, or $N(C_1\text{-}C_6$ alkyl) $(C_1\text{-}C_{12}$ alkyl), wherein said $C_1\text{-}C_{12}$ alkyl may be substituted by NC_2H_5, or NH benzyl which may be substituted by one or two bromo, chloro, fluoro, NC_2H_5 phenyl or morpholinopropyl;

(i) when R_3 and R_4 are hydrogen and R_5 is nitrophenyl, then A is not NHR_2 wherein R_2 is C_1-C_{12} alkyl which may be substituted by two hydroxy, or R_2 is phenyl or benzyl;

(j) when R_3 is chloro or O(C_1-C_6 alkyl), R_4 is hydrogen, and A is NR_1R_2 wherein R_1 and R_2 are independently hydrogen or C_1-C_6 alkyl, then R_5 is not chlorophenyl; and

(k) when R_3 is hydrogen, A is benzyl or phenethyl, and R_4 is fluoro, chloro, bromo or iodo, then R_5 is not 5'-deoxy-ribofuranosyl or 5'-amino-5'-deoxy-ribofuranosyl.

Preferred compounds of the formula I of the invention are those wherein R_1 is C_1-C_4 alkyl, (C_2-C_4 alkylene)O(C_1-C_4 alkyl), or C_2-C_4 hydroxyalkyl; those wherein R_2 is C_1-C_5 alkyl, benzyl, phenylethyl, or benzyl substituted by one or two of chloro, fluoro, methyl, ethyl, methoxy, ethoxy or t-butyl, or by one of trifluoromethyl; (2-thienyl)methyl; (2-thienyl)ethyl; (2-furanyl)methyl; 2-(4-chlorothienyl)methyl; (2-benzofuranyl)methyl; (2-benzothienyl)methyl; (2-thiazolyl)methyl; or (2-benzothiazolyl)methyl; those wherein R_1 is C_1-C_4 alkyl, C_2-C_4 hydroxyalkyl or (C_2-C_4 alkyl)-O-(C_1-C_2 alkyl); those wherein R_3 is hydrogen, methyl, ethyl, methoxy, fluoro or chloro; those wherein R_4 is methylthio, methylsulfonyl, methylsulfinyl, hydrogen, methyl, ethyl, or n-propyl, and those wherein R_5 is phenyl substituted by two or three substituents.

More specific compounds of the formula I are those wherein A is NR_1R_2, $NHCHR_1R_2$, or $OCHR_1R_2$, wherein R_1 is C_1-C_6 alkyl, which may be substituted by one of hydroxy, fluoro or C_1-C_2 alkoxy, and may contain one double or triple bond, and R_2 is benzyl or C_1-C_5 alkyl which may contain one double or triple bond, wherein said C_1-C_6 alkyl or the phenyl in said benzyl may be substituted by fluoro, C_1-C_6 alkyl, or C_1-C_6 alkoxy; and those wherein A is $CR_1R_2R_{11}$ wherein R_1 is C_1-C_6 alkyl which may be substituted by one C_1-C_6 alkoxy or hydroxy, R_2 is benzyl or C_1-C_6 alkyl wherein said C_1-C_6 alkyl or the phenyl in said benzyl may be substituted by one C_1-C_6 alkyl, C_1-C_6 alkoxy, fluoro, chloro or bromo, and R_{11} is hydrogen or fluoro.

More specific compounds of the formula I include those wherein R_2 is (C_1-C_4 alkylene)aryl wherein said aryl is phenyl, thienyl, benzofuranyl, furanyl, benzothienyl, thiazolyl, pyridyl or benzothiazolyl.

More specific compounds of the formula I further include those wherein R_2 is benzyl para-substituted by one of ethyl, t-butyl, methoxy, trifluoromethyl, nitro, fluoro chloro, or methyl.

Other more specific compounds of the formula I include those wherein R_2 is attached through a methylene or ethylene bridge to quinolyl, pyrrolyl, pyrrolidinyl, pyridyl, tetrahydropyranyl, cyclopropyl, piperidinyl, or benzyl-piperidinyl.

More specific compounds (I) further include those wherein R_1 or R_2 is C_1-C_6 alkyl which may be substituted by one of hydroxy, methoxy, ethoxy, chloro, fluoro, $OC(O)CH_3$, $OC(O)NHCH_3$, or $C(O)NH_2$.

Other more specific compounds (I) include those wherein R_2 is C_1-C_6 alkyl substituted by two of methoxy or ethoxy, or one of $COOC_2H_5$, methylthio, or phenyl.

Other more specific compounds (I) include those wherein A is NR_1R_2 or CHR_1R_2 in which R_1 and R_2 are taken together with N or CH to form a 5- or 6-membered ring having one more nitrogen, sulfur, and/or one oxygen, e.g. pyrrolidinyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, thiazolyl, isoxazolyl, thiadiazolyl, oxadiazolyl, pyridyl, pyrazinyl or pyrimidyl.

Other more specific compounds (I) includes those wherein A is $NHCHR_1R_2$ or $OCHR_1R_2$ in which CHR_1R_2 is a 5- or 6-membered ring which may contain one oxygen or sulfur, e.g. tetrahydrofuranyl, tetrahydrothiafuranyl and cyclopentanyl.

Most preferred compounds of the formula I include

3-{(4-methyl-benzyl)-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propan-1-ol;

diethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

2-{butyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethanol;

dibutyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl}-amine;

butyl-ethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-ethyl-[6-methyl-3-methylsulfonyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-cyclopropylmethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

di-1-propyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

diallyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-ethyl-[6-chloro-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-ethyl-[6-methoxy-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

propyl-ethyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

4-(1-ethyl-propyl)-6-methyl-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine;

2-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-ylamine]-butan-1-ol;

[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo-[3,4-d]pyrimidin-4-yl]-(1-methylpropyl)amine; and

4-(1-methoxymethylpropoxy)-3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine.

The invention also relates to a pharmaceutical composition for the treatment of illnesses induced or facilitated by corticortropin releasing factor which comprises a compound of the formula I as defined above in an amount effective in the treatment of said illnesses, and a pharmaceutically acceptable carrier, and a pharmaceutical composition for the treatment of inflammatory disorders, such as arthritis, asthma and allergies; anxiety; depression; fatigue syndrome; headache; pain; cancer; irritable bowel syndrome, including Crohn's disease, spastic colon and irritable colon; immune dysfunction; human immunodefiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease; gastrointestinal disease; eating disorders such as anorexia nervosa; hemorrhagic stress; drug and alcohol withdrawal symptoms; drug addiction; stress-induced psychotic episodes; and fertility problems, which comprises a compound of the formula I as defined above in an amount effective in the treatment of said disorders, and a pharmaceutically acceptable carrier. Preferred compositions of the invention are those containing preferred compounds of formula I as described above.

The invention further relates to a method for the treatment of illnesses induced or vacilitated by corticotropin releasing factor by administering to a subject in need of

such treatment a compound of formula I as defined above in an amount effective in such treatment, and a method for the treatment of inflammatory disorders, such as arthritis, asthma and allergies; anxiety; depression; fatigue syndrome; headache; pain; cancer; irritable bowel syndrome, including Crohn's disease, spastic colon and irritable colon; immune dysfunction; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease; gastrointestinal diseases; eating disorders such as anorexia nervosa; hemorrhagic stress; drug and alcohol withdrawal symptoms; drug addiction; stress-induced psychotic episodes; and fertility of such treatment a compound of formula I as defined above in an amount effective in such treatment. Preferred methods of the invention are those administering a preferred compound of the formula I as described above.

Although R_5 includes cycloalkyl and bicycloalkyl containing oxygen atoms in the rings and hydroxyl and hydroxymethyl substituents on the rings, the compounds of formula I do not include sugar groups $C_nH_{2n-1}O_{n-1}$, such as $C_5H_9O_4$ (ribofuranosyl) and $C_6H_{11}O_5$ (ribopyranosyl), which have more than two hydroxy groups directly or indirectly attached to the ring or rings in the sugar group.

Whenever reference is made to alkyl, this includes straight and branched chain alkyl, unless otherwise indicated.

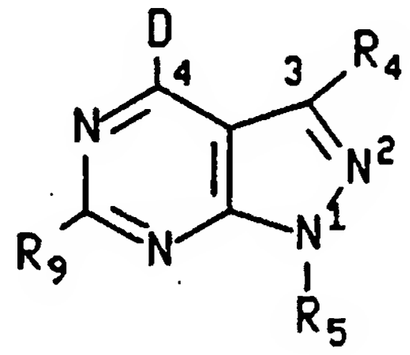
Whenever reference is made herein to 3-to 8-membered cycloakyl or 9- to 12-membered bicycloakyl containing one to three of O, S or N-Z, it is understood that the oxygen and sulfer ring atoms are not adjacent to each other. The three membered cycloalkyl has just one O, S or N-Z. An example of a six-membered cycloalkyl having O and N is morpholinyl.

Whenever R_2 or R_5 is a heterocyclic group, the attachment of the group is through a carbon atom.

Whenever reference is made herein to C_1-C_4 alkyl or C_1-C_6 alkyl which "may contain one or two double or triple bonds" in the definitions of R_1, R_2 and R_3, it is understood that at least two carbons are present in the alkyl for one double or triple bond, and at least four carbons for two double and triple bonds.

Whenever an alkoxy group, e.g. in the definitions of R_1 and R_2, may have a double or triple bond, it is understood that such double or triple bond is not directly attached to the oxygen.

The compounds of formula I wherein A is NR_1R_2, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$ or $NHNR_1R_2$, and R_2 is hydrogen, C_1-C_6 alkyl or chloro (hereafter R_9) may be prepared by reaction of a compound of the formula



II

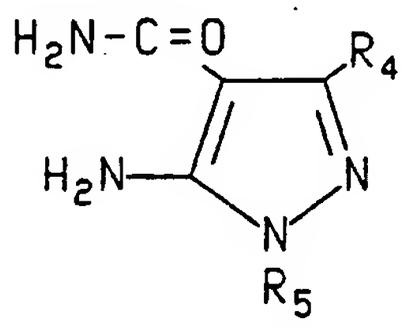
wherein D is Cl, and R_4, R_5 and R_6 are as defined above with reference to formula I, with a compound of the formula AH wherein A is as defined immediately above. The reaction is carried out in a solvent in the presence of a base at a temperature of between about 0° to about 150°C. Suitable solvents are organic solvents such as acetonitrile, dimethylsulfoxide, acetone, C_2-C_{15} alkyl alcohol, tetrahydrofuran, chloroform, benzene, xylene or tuluene, preferably acetonitrile or dimethylsulfoxide.

When A is NR_1R_2, $NHNR_1R_2$, or $NHCR_1R_2R_{11}$, an excess of AH is used. Other bases such as potassium carbonate or tri-(C_1-C_6)alkyl amine may be used instead. The reaction is carried out at a temperature of about 75° to 150°C. When the reaction is carried out in the presence of a base, such as sodium hydride or potassium C_1-C_4 alkoxide, a molar equivalent of the amine is used. When A is $OCR_1R_2R_{11}$ or $SCR_1R_2R_{11}$, a base which is capable of deprotonation of AH may be used, such as an alkali metal hydride such as sodium or potassium hydride, or an organometallic base such as sodium diisopropylamide, sodium bis(trimethylsily)amide, lithium diisopropylamide, lithium bis(trimethylsily)amide, sodium C_1-C_4 alkoxyde or n-butylithium. The solvent used is dry tetrahydrofuran, dimethylsulfoxide, methylene chloride, or tuluene, and the reaction temperature is between about -78°C and the reflux temperature of the reaction mixture, preferably 0°C to 80°C.

The compounds of formula II wherein D is chloro may be prepared by reacting the corresponding 4-hydroxy compound of formula III (not shown) with a molar excess of phosphorus oxychloride or thionyl chloride at temperatures between about 60 to 140°C, conveniently at the reflux temperature of the reaction mixture. When the reaction is carried out in a solvent, suitable solvents are halogenated alkanes, such as

methylene chloride or chloroform. The reaction may be in the presence of a base such as N, N-diethylaniline, trimethylamine or potassium carbonate.

The compounds of the formula III as defined above may be prepared by reaction of a compound of the formula



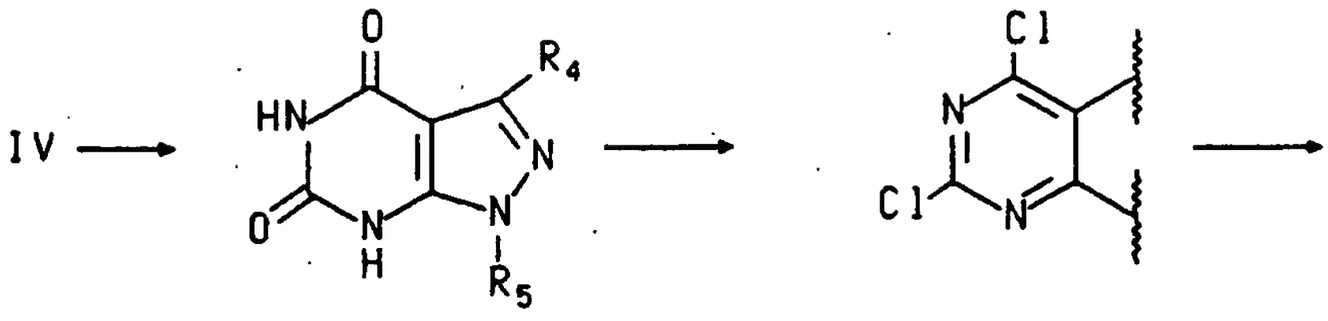
IV

wherein R_4 and R_5 are as defined with reference to formula I, with a compound of the formula R_9CNH_2 (V) wherein R_9 is as defined above. This reaction is conveniently carried out in the absence of a solvent at temperatures between about 100°C to 250°C.

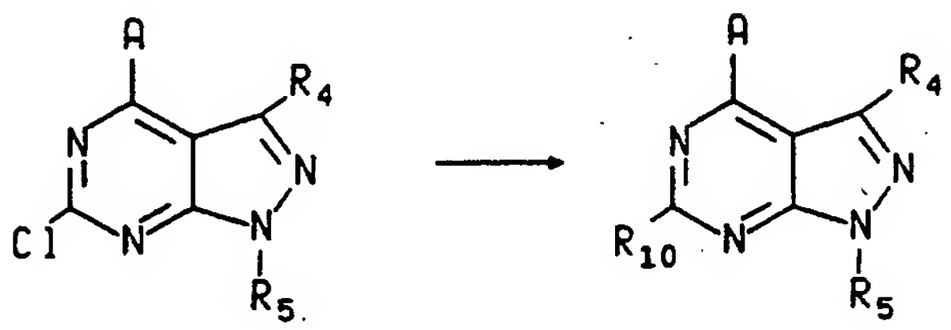
The compounds of formulae IV and V are either readily available or may be prepared by conventional methods.

As depicted in Scheme 1, the compounds of formula I wherein R_3 is the groups other than R_9 (hereafter R_{10}) may be prepared by reacting a compound of the formula I wherein R_3 is chloro, having formula VIII in Scheme 1, with a nucleophile of the formula $R_{10}H$ with or without an organic or inorganic base. Suitable bases include sodium, sodium hydride, and alkali metal hydroxide such as potassium hydroxide, and weaker bases such as potassium carbonate or triethylamine. The latter are generally used when $R_{10}H$ is alkanol, C_1-C_6 alkanethiol, an amine, e.g. $NH(C_1$-C_6 alkyl), or tetrahydrobutyl ammonium fluoride. Suitable solvents are dimethylsulfoxide, acetonitrile, C_1-C_5 alkyl alcohol, tetrahydrofuran, benzene, toluene or methylene chloride.

Scheme I



VI VII



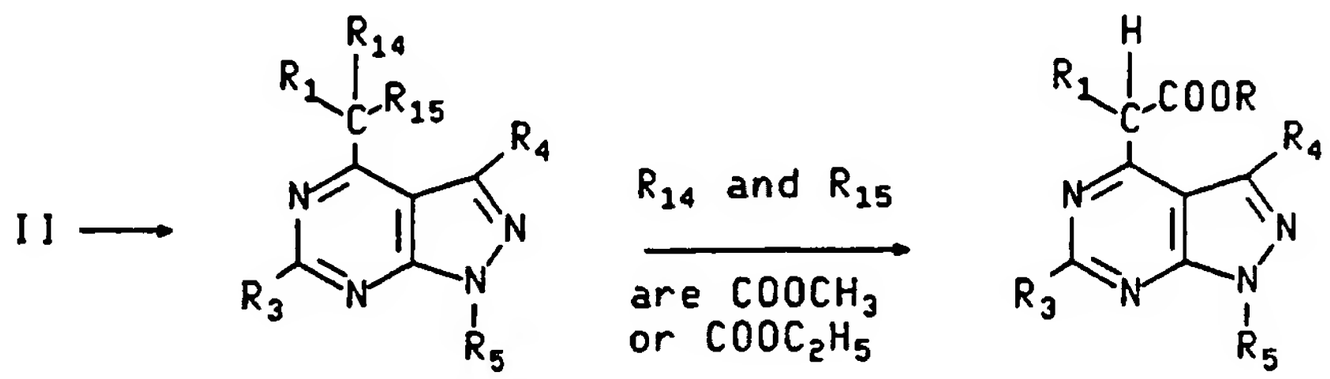
VIII IX

The compound of formula IV as defined above is reacted with an excess of urea at reflux temperature to form a compound of the formula VI. The compound of formula VII is formed on reaction of a compound VI with phosphorus oxychloride or thionyl chloride at temperatures between about 70°C to 140°C and conveniently the reflux temperature of the reaction mixture, in the optional presence of a base such as N, N-diethylaniline. The compound of formula VIII is formed on reaction of compound VII with AH under the same reaction conditions as described above for the reaction of compound II with AH.

The compounds of the formula I wherein A is $CR_1R_2R_{11}$ or $C(=CR_{12}R_{13})R_2$ may be prepared, as depicted in Scheme 2 below, from corresponding compounds of the formula II wherein R_4 and R_5 are as defined above, and R_9 is R_3 as defined with reference to formula I by reaction with a compound of the formula $CHR_1R_{14}R_{15}$ wherein R_1 is as defined with reference to formula I, and R_{14} and R_{15} are each independently $COO(C_1\text{-}C_2$ alkyl), $CO(C_1\text{-}C_2$ alkyl) or CN, to form the compound of formula IA. The reaction is carried out in the presence of a base such as sodium hydride, potassium $C_1\text{-}C_5$ alkoxide, sodium or lithium bis(trimethylsilyl) amide, and sodium or lithium diisopropylamide, in a reaction inert solvent such as dimethylsulfoxide, acetonitrile, C_2-

C_6 alkyl alcohol, or N-methyl-pyrrolidone, preferably dimethylsulfoxide. The reaction is preferably carried out at elevated temperatures of about 100°C to 180°C.

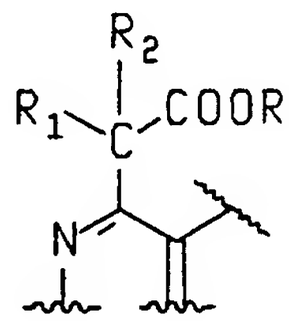
Scheme 2



IA IB

The compounds of formula IB may be prepared by reaction of those compounds of formula IA wherein R_{14} and R_{15} are each COOR wherein R is methyl or ethyl, by reaction with diisobutylaluminum hydride in a reaction inert solvent at temperatures of about -78°C to 40°C, preferably about -20° to 25°C. Suitable solvents are toluene, benzene and tetrahydrofurane, preferably toluene.

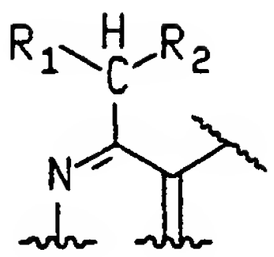
The compounds of formula IB may be converted into corresponding compounds of the formula



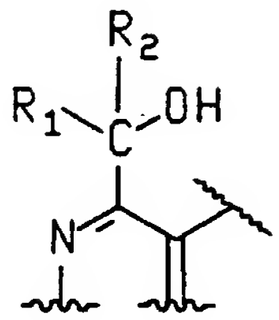
IC

by reaction with a compound of the formula R_2L wherein R_2 is as defined with reference to formula I, and L is a leaving group such as chloro, bromo, iodo, mesylate or tosylate, in the presence of a base and a reaction inert solvent at temperatures of about 0° to 50°C, preferably room temperature. Suitable solvents include dimethylsulfoxide, C_2-C_6 alkyl alcohol, tetrahydrofuran, methylene chloride and dioxane.

The compounds of the formulae



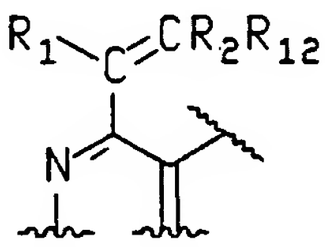
ID



IE

may be prepared from the corresponding compounds of formula IC by reaction with lithium iodide in a solvent such as dimethylformamide, dimethyl sulfoxide and dioxane at temperatures of about 50°C to 200°C, preferably about 100° to 150°C. The reaction to form compound IE is in the presence of air.

When R_2 in above formula IE is a group of the formula CHR_2R_{12}, then the compounds of formula IE may be further converted to corresponding compounds of the formula



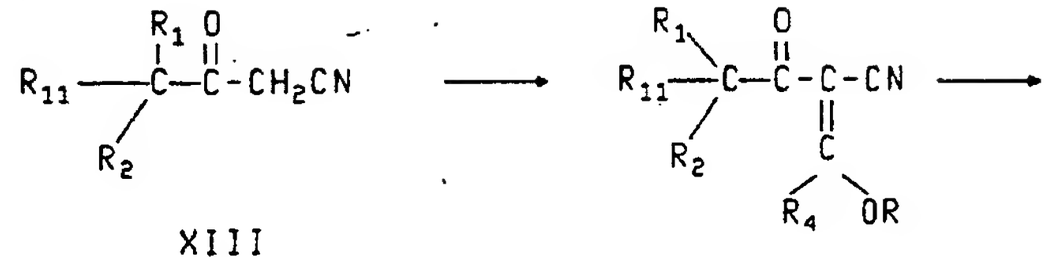
IF

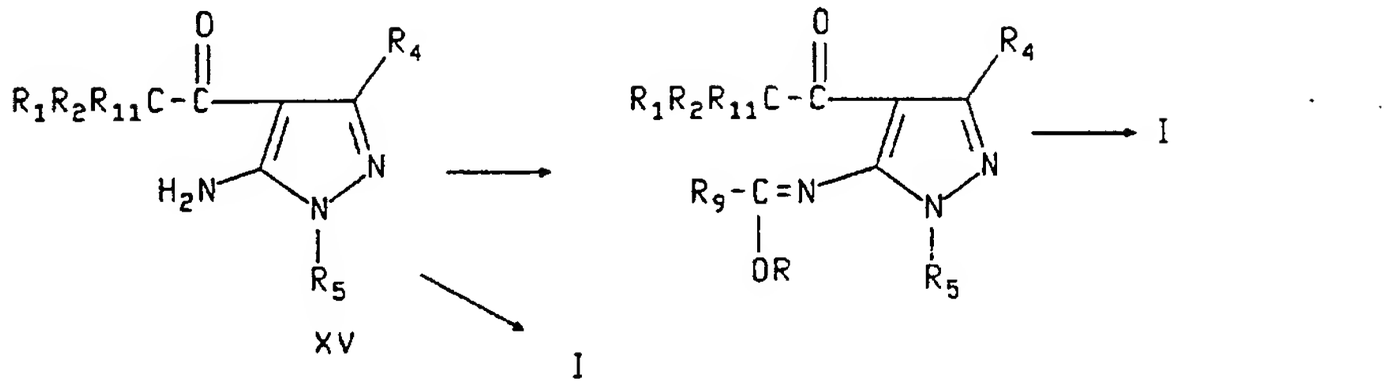
using the same reaction conditions as used for the conversion of compounds IC to ID.

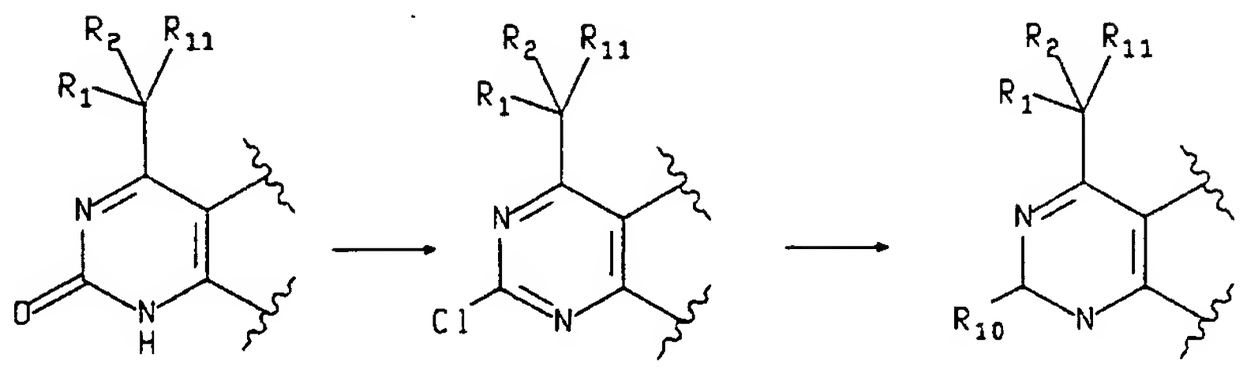
The compounds of formula I wherein A is $CR_1R_2R_{11}$ or $C(=CR_2R_{12})R_1$ may be prepared as shown in Scheme 3.

The compounds of formula XIV may be prepared by reaction of the trialkoxy compound $R_4C(OR)_3$ wherein R is C_1-C_2 alkyl and R_4 is as defined with reference to formula I with the compound of formula XIII, wherein R_2 and R_{11} may be replaced by $=CR_2R_{12}$, in the presence of acetic anhydride and in the optional presence of a solvent such as ethyl acetate, methylene chloride, chloroform, or toluene. The reaction is carried out at temperatures of about 30°C to 150°C, preferably 80°C to 120°C. The compound of formula XV is obtained by reacting the corresponding compound of formula XIV with a hydrazine of the formula R_5NHNH_2, wherein R_5 is as defined with reference to formula I, in a solvent such as a C_1-C_4 alkyl alcohol or acetonitrile at a temperature of about 60° to 120°C, preferably reflux temperature.

Scheme 3







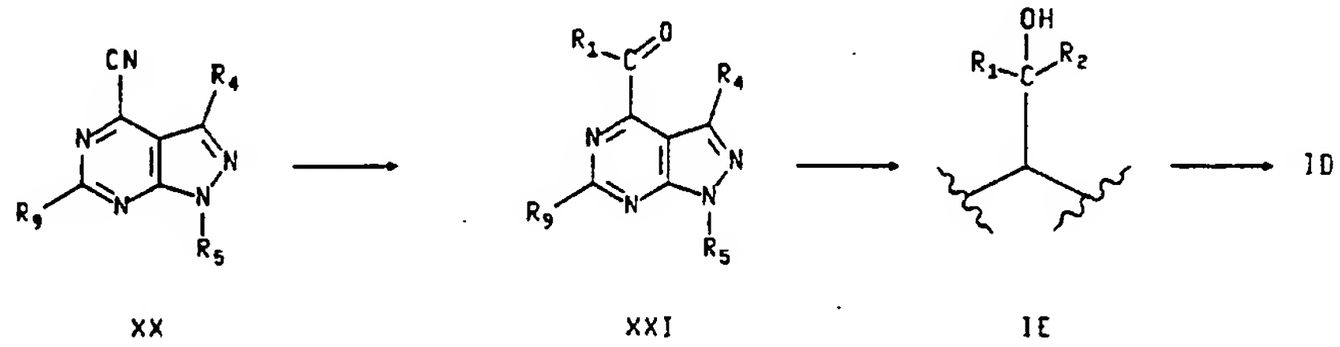
The compounds of formula I wherein A is $CR_1R_2R_{11}$ may be obtained by reacting the corresponding compound of formula XV with R_9CONH_2, wherein R_9 is hydrogen, C_1-C_6 alkyl or amino, in the presence of ammonium chloride by heating at reflux temperatures of about 240°C. Alternatively, the compound of formula XVI may be prepared from the corresponding compound of formula XV with $R_9C(OR)_3$ wherein R is C_1-C_2 alkyl using reaction conditions similar to those used for the preparation of compounds of the formula II from the compounds of formula III, as described above.

The compounds of formula XV may be reacted with an excess of urea at reflux temperatures to form a compound of the formula XVII. Conversion of compounds XVII

to XVIII and XIX may be effected by the same procedure as in Scheme 1 for the conversion of compounds VII to VIII and IX, respectively.

The compounds of formula I wherein A is $CR_1R_2R_{11}$, $C(=CR_2R_{12})R_1$, $CR_2R_{11}NHR_1$, $CR_2R_{11}SR_1$, or $C(O)R_2$, and R_3 is R_9 as defined above with reference to formula II, may be prepared as depicted in Scheme 4.

Scheme 4



The compounds of formula XX, wherein R_4, R_5, and R_9 are as defined above, prepared by reacting the corresponding compound of formula II with potassium cyanide in dimethylsulfoxide, are reacted with a Grignard reagent containing group R_1 as defined above to form the compound of formula XXI. Further reaction of the compound of formula VII with a Grignard reagent containing group R_2 as defined above provides the compound of formula IC. Corresponding compounds of formula ID wherein B is $CR_1R_2R_{11}$ or $C(=CR_2R_{12})R_1$ may be prepared by conventional methods.

The compounds of formula I wherein group R_1, R_2, R_3, R_4 or R_5 contains a sulfoxy or a sulfinyl group may be obtained by oxidation of the corresponding sulfur compound, as is known by the skilled person.

When the compounds of the invention contain one or more chiral centers, it is understood that the invention includes the racemic mixture and the individual diastereomers and enantiomers of such compounds.

The pharmaceutically acceptable acid addition salts are prepared in a conventional manner by treating a solution or suspension of the free base of formula I with one chemical equivalent of a pharmaceutically acceptable acid. Conventional concentration or crystallization techniques are employed in isolating the salts. Illustrative of suitable acids are acetic, lactic, succinic, maleic, tartaric, citric, gluconic, ascorbic, benzoic, cinnamic, fumaric, sulfuric, phosphoric, hydrochloric, hydrobromic, hydroiodic, sulfamic, sulfonic acids such as methanesulfonic, benzene sulfonic, p-toluenesulfonic, and related acids.

The novel compound of the invention of formula I may be administered alone or in combination with pharmaceutically acceptable carriers, in either single or multiple, e.g. up to three, doses. Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. The pharmaceutical compositions formed by combining the novel compounds of formula I and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms such as tablets, powders, lozenges, syrups, injectable solutions and the like. These pharmaceutical compositions can, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus, for purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard filled gelatin capsules. Preferred materials for this include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if desired, emulsifying or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin and combinations thereof.

For parenteral administration, solutions of the novel compound of formula I in sesame or peanut oil, aqueous propylene glycol, or in sterile aqueous solution may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Additionally, it is possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may be done by way of creams, jellies, gels, pastes, and ointments, in accordance with standard pharmaceutical practice.

The effective dosage for the compound of formula I depends on the intended route of administration and other factors such as age and weight of the patient, as generally known to a physician. The dosage also depends on the illness to be treated. The daily dosage will generally range from about 0.1 to 50 mg/kg of the body weight of the patient to be treated. For treatment of inflammatory diseases about 0.1 to about 100 mg/kg will be needed, and for Alzheimer's disease, about 0.1 to about 50 mg/kg, as well as for gastrointestinal diseases, anorexia nervosa, hemorrhagic stress, drug and alcohol withdrawal symptoms, fertility problems, etc.

The methods for testing the compounds of formula I for their CRF antagonist activity are as described in Endocrinology, 116, 1653-1659 (1985) and Peptides 10, 179-188 (1989), which determine the binding affinity of a test compound to a CRF receptor. The binding affinity for the compounds of formula I, expressed as IC_{50} values, generally ranges from about 0.2 nanomolar to about 10 micromolar.

The following Examples illustrate the invention. The following abbreviations are used: Ph=phenyl, Me=methyl, t-Bu=t-butyl, Et=ethyl, Pr=propyl.

Example 1

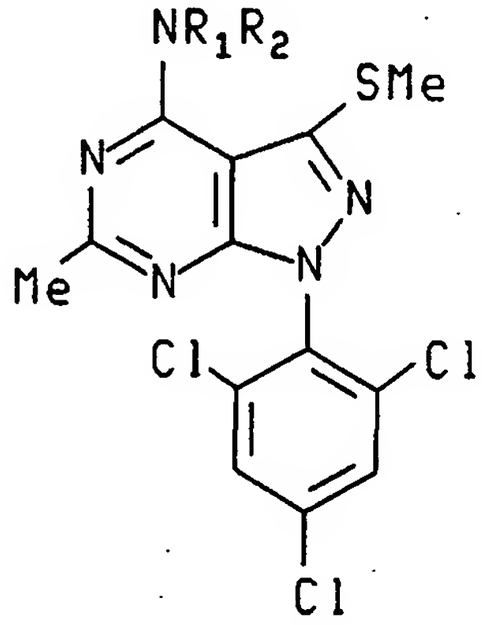
3-{(4-methylbenzyl)-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propanol

A mixture of 4-chloro-3-methylsulfanyl-6-methyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (788 mg, 2 mmol) and 3-(p-methylbenzyl)amino-1-propanol (716 mg, 4 mmol) in 10 ml of acetonitrile was heated at reflux for 4 hours. The mixture was cooled, quenched with water and dilute hydrogen chloride and extracted with ethyl acetate. The organic layer was washed with aqueous sodium bicarbonate and brine, separated, dried and concentrated to give 953 mg of the title compound as an off-white glass form. The material was purified through silica gel column chromatography using chloroform as eluent to give the title compound as a white glass form. ^1H NMR ($CDCl_3$): 1.79 (m, 2H), 2.38 (s, 3H), 2.52 (s, 3H), 2.54 (s, 3H), 3.56 (t, 2H), 3.86 (t, 2H), 5.12 (s, 2H), 7.20 (s, 4H), 7.51 (s,2H) ppm. ^{13}C NMR ($CDCl_3$): 16.20, 21.13, 25.53, 29.64, 43.51, 53.88, 58.24, 127.78, 128.77, 129.33, 133.51, 136.18, 137.41, 142.93, 159.13, 164.89 ppm. IR(KBr): 3350, 2935, 1540 cm^{-1}. Anal. calc. for $C_{24}H_{24}N_5OSCl_3$: C, 53.69; H, 4.50; N, 13.04; found: C, 53.33, H, 4.44, N, 12.84.

Example 2

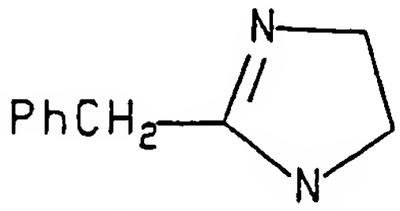
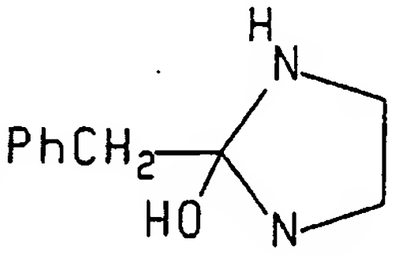
The following compounds were prepared starting with the appropriate amine and 4-chloro-3-methylsulfanyl-6-methyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine and employing the procedure of Example 1.

Table 1



NR_1R_2	^1H NMR ($CDCl_3$) ppm
$PhCH_2N(CH_2)_2OH$	2.48(s,3H), 2.52(s,3H), 3.7-3.9(m,4H), 5.14(s,2H), 7.2-7.4(m,5H), 7.48(s,2H)
$PhCH_2N(CH_2)_3OH$	1.80(m,2H), 2.52(s,3H), 2.54(s,3H), 3.56(t,2H), 3.88(t,2H), 5.17(s,2H), 7.30-7.40(m,5H), 7.51(s,2H)
$Ph(CH_2)_2N(CH_2)_3OH$	1.90(,2H), 2.49(s,3H), 2.63(s,3H), 3.07(m,2H), 3.57(t,2H), 3.92(t,2H), 4.12(t,2H), 4.4(brs,1H), 7.2-7.5(m,5H), 7.51(s,2H)
p-Cl-$PhCH_2N(CH_2)_3OH$	1.82(m,2H), 2.52(s,3H), 2.55(s,3H), 3.57(q,2H), 3.86(t,2H), 5.12(s,2H), 7.2-7.4(m,4H), 7.51(s,2H)
p-O_2N-$PhCH_2N(CH_2)_3OH$	1.88(m,2H), 2.50(s,3H), 2.53(s,3H), 3.61(t,2H), 3.89(t,2H), 5.23(s,2H), 7.45-7.55(m,2H), 7.50(s,2H), 8.24(d,2H)

NR_1R_2	^1H NMR ($CDCl_3$) ppm
p-MeO-$PhCH_2N(CH_2)_3OH$	1.71(m,2H), 2.49(s,3H), 2.52(s,3H), 3.5(t,2H), 3.80(s,3H), 3.82(t,2H), 5.05(s,2H), 6.88(d,2H), 7.20(d,2H), 7.5(s,2H)
p-F_3C-$PhCH_2N(CH_2)_3OH$	1.82(m,2H), 2.5(s,3H), 2.52(s,3H), 3.55(m,2H), 3.85(t,2H), 5.15(s,2H), 7.4(d,2H), 7.5(s,2H), 7.6(d,2H)
p-Cl-$PhCH_2N(CH_2)_4OH$	1.45-1.70(m,2H), 1.70-1.90(m,2H), 2.49(s,3H), 2.59(s,3H), 3.62-3.75(m,4H), 5.04(s,2H), 7.2-7.4(m,4H), 7.50(s,2H)
p-t-Bu-$PhCH_2N(CH_2)_3OH$	1.34(s,9H), 1.75-1.85(m,2H), 2.51(s,3H), 2.55(s,3H), 3.50-3.51(m, 2H), 3.86(t,2H), 5.14(s,2H), 7.15-7.45(m,4H), 7.51(s, 2H)
o-Me-$PhCH_2N(CH_2)_3OH$	1.8(m,2H), 2.2(s,3H), 2.45(s,3H), 2.55(s,3H), 3.6(t,2H), 3.95(t,2H), 5.1(s,2H), 7.1-7.3(m,4H), 7.45(s,2H)
2,5-di-Me-$PhCH_2N(CH_2)_3OH$	1.75(m,2H), 2.20(s,3H), 2.25(s,3H), 2.45(s,3H), 2.50(s,3H), 3.52(t,2H), 3.90(t,2H), 5.04(s,2H), 6.90(s,1H), 6.92-7.10(m,2H), 7.45(s,2H)
2,4,6-tri-Me-$PhCH_2N(CH_2)_3OH$	1.59(m,2H), 2.2(s,6H), 2.28(s,3H), 2.50(s,3H), 2.60(s,3H), 3.48(t,2H), 3.68(t,2H), 4.4(brs, 1H), 5.1(s,2H), 6.82(s,2H), 7.50(s,2H)
o-F-$PhCH_2N(CH_2)_3OH$	1.82(m,2H), 2.45(s,3H), 2.46(s,3H), 3.56(t,2H), 3.88(t,2H), 5.20(s,2H), 7.0-7.3(m,4H), 7.47(s,2H)
p-Et-$PhCH_2N(CH_2)_3OH$	1.23(t,3H), 1.7-1.85(m,2H), 2.48(s,3H), 2.51(s,3H), 2.64(q,2H), 3.5-3.6(m,2H), 3.8-3.95(m,2H), 5.1(s,2H), 7.1-7.3(m,4H), 7.48(s,2H)
p-F-$PhCH_2N(CH_2)_3OH$	1.8(m,2H), 2.50(s,3H), 2.58(s,3H), 3.6(t,2H), 3.88(t,3H), 5.1(s,2H), 7.0-7.3(m,4H), 7.5(S,2H)
2-thienyl-$CH_2N(CH_2)_3OH$	1.9(m,2H), 2.55(s,3H), 2.60(s,3H), 3.6(t,2H), 3.93(t,2H), 5.25(s,2H), 7.0(dd,1H), 7.05(m,1H), 7.28(dd,1H), 7.48(s,2H)

NR_1R_2	^1H NMR ($CDCl_3$) ppm
2-thienyl-$(CH_2)_2N(CH_2)_3OH$	1.95(m,2H), 2.50(s,3H), 2.65(s,3H), 3.35(m,2H), 3.62(t,2H), 4.0(t,2H), 4.15(m,2H), 6.9(m,2H), 7.15(d,1H), 7.5(s,2H)
$Ph(CH_2)_2NCH_2CH(OEt)_2$	1.1-1.3(m,6H), 2.47(s,3H), 2.63(s,3H), 3.05(t,2H), 3.5-3.65(m,2H), 3.65-3.82(m,2H), 3.89(d,2H), 4.22(t,2H), 4.82(t,1H), 7.1-7.4(m,5H), 7.50(s,2H)
2-quinolinyl-$CH_2N(CH_2)_3OH$	2.05(m,2H), 2.49(s,3H), 2.54(s,3H), 3.65(t,2H), 3.99(t,2H), 5.52(s,2H), 7.51(s,2H), 7.52-7.9(m,4H), 8.21(t,2H)
2,6-di-Cl-$PhCH_2N(CH_2)_3OH$	1.58(m,2H), 2.54(s,3H), 2.67(s,3H), 3.52(t,2H), 3.84(t,2H), 5.40(s,2H), 7.2-7.4(m,3H), 7.52(s,2H)
thiazolidinyl	2.55(s,3H), 2.65(s,3H), 3.15(t,2H), 4.25(t,2H), 5.0(s,2H), 7.5(s,2H)
p-Cl-$PhCH_2N(CH_2)_2COOEt$	1.22(t,3H), 2.50(s,3H), 2.58(s,3H), 2.76(t,2H), 3.96(t,2H), 4.10(q,2H), 5.08(s,2H), 7.2-7.4(m,4H), 7.51(s,2H)
1-pyrrolidinyl-$(CH_2)_2N(CH_2)_2OH$	1.7(m,4H), 2.0(m,2H), 2.45(s,3H), 2.62(s,3H), 2.65(m,4H), 2.95(t,2H), 3.6(t,2H), 4.0(m,4H), 7.48(s,2H)
p-$MePhCH_2N(CH_2)_3SMe$	2.0(m,2H), 2.1(s,3H), 2.35(s,3H), 2.5(s,3H), 2.6(s,3H), 3.75(m,2H), 5.05(s,2H), 7.18(q, 4H), 7.5(s,2H)
	2.54(s,3H), 2.64(s,3H), 4.05(m,2H), 4.2-4.3(m,4H), 7.05-7.25(m,5H), 7.50(s,2H)
	2.47(s,3H), 2.68(s,3H), 3.55(s,2H), 3.5-3.65(m,2H), 3.8(m,2H), 6.15(brs, 1H), 6.30(brs, 1H), 7.15-7.32(m,5H), 7.5(s,2H)
3-quinolinyl-$CH_2NCH_2N(CH_2)_3OH$	1.85(m,2H), 2.50(s,3H), 2.52(s,3H), 3.60(t,2H), 3.89(t,2H), 5.13(s,2H), 7.25(d,2H), 7.50(s,2H), 8.59(d,2H)

NR_1R_2	^1H NMR ($CDCl_3$) ppm
2-quinolinyl-$CH_2N(CH_2)_3OH$	1.88(m,2H), 2.50(s,3H), 2.51(s,3H), 3.60(t,2H), 3.95(t,2H), 5.27(s,2H), 7.25(m,1H), 7.32(d,1H), 7.50(s,2H), 7.70(t,1H), 8.62(d,1H)
$MeCON(CH_2)_2OH$	2.1(s,3H), 2.5(s,3H), 2.68(s,3H), 3.95(q,2H), 4.35(t,2H), 6.15(t,1H), 7.47 (s,2H)
imidazolyl	2.68(s,3H), 2.75(s,3H), 7.33(s,1H), 7.57(s,2H), 7.92(s,1H), 8.69(s,1H)
2-pyridyl-$CH_2N(CH_2)_3OMe$	2.0-2.1(m,2H), 2.45(s,3H), 2.56(s,3H), 3.25(s,3H), 3.44(t,2H), 3.90(t,2H), 5.2(s,2H), 7.18(m,1H), 7.30(m,1H), 7.50(s,2H), 7.64(t,2H), 8.58(m,1H)
2-furanyl-CH_2-$N(CH_2)_2$-SH	2.48(s,3H), 2.62(s,3H), 2.80(m,2H), 3.90(t,2H), 5.03(s,2H), 6.32(s,2H), 7.36(s,1H), 7.47(s,2H)
3-pyridyl-$CH_2N(CH_2)_3OH$	1.85(m,2H), 2.49(s,3H), 2.53(s,3H), 3.59(t,2H), 3.86(t,2H), 5.13(s,2H), 7.3-7.4(m,1H), 7.48(s,2H), 7.71(m,1H), 8.55-8.62(m,2H)
2-(4-chlorothienyl)-$(CH_2)_2N(CH_2)_3OH$	1.90(m,2H), 2.54(s,3H), 2.62(s,3H), 3.63(t,2H), 3.90(t,2H), 5.07(s,2H), 6.76(d,1H), 6.84(d,1H), 7.49(s,2H)
4-(1-benzylpiperidinyl)-$CH_2N(CH_2)_3OH$	1.3-1.5(m,2H), 1.5-1.75(m,2H), 1.75-2.1(m,5H), 2.42(s,3H), 2.62(s,3H), 2.8-3.0(m,2H), 3.5(s,2H), 3.55(t,2H), 3.80(d,2H), 3.89(t,2H), 7.2-7.4(m,5H), 7.48(s,2H)
2-benzofuranyl-$CH_2N(CH_2)_3OH$	1.87(m,2H), 2.54(s,3H), 2.59(s,3H), 3.62(t,2H), 4.01(t,2H), 5.31(s,2H), 6.70(s,1H), 7.2-7.4(m,2H), 7.52(s,2H), 7.4-7.6(m,2H)
2-furanyl-$CH_2N(CH_2)_3OH$	1.77(m,2H), 2.50(s,3H), 2.61(s,3H), 3.55(t,2H), 3.90(t,2H), 4.51(brs,1H), 5.13(s,2H), 6.36(m,2H), 7.41(m,1H), 7.50(s,2H)
2-furanyl-NH	2.55(s,3H), 2.67(s,3H), 4.88(d,2H), 6.19(t,1H), 6.37(m,2H), 7.42(d,1H), 7.51(s,2H)

NR_1R_2	^1H NMR ($CDCl_3$) ppm
2-benzofuranyl-$CH_2N(CH_2)_2OH$	2.57(s,3H), 2.61(s,3H), 3.86(t,2H), 4.01(t,2H), 5.32(s,2H), 6.77(s,1H), 7.2-7.4(m,2H), 7.52(s,2H), 7.45-7.60(m,2H)
p-Cl-Ph$CH_2N(CH_2)_2OH$	2.5(s,3H), 2.55(s,3H), 3.8(s,4H), 5.1(s,2H), 7.2-7.4(m,4H), 7.5(s,2H)
2-benzothienyl-$CH_2N(CH_2)_3OH$	1.90(m,2H), 2.50(s,3H), 2.58(s,3H), 3.6(t,2H), 3.95(t,2H), 5.3(s,2H), 7.2-7.4(m,3H), 7.5(s,2H), 7.7-7.85(m,2H)
3-quinolinyl-$CH_2N(CH_2)_3OH$	1.87(m,2H), 2.49(s,3H), 2.51(s,3H), 3.60(t,2H), 3.92(t,2H), 5.30(s,2H), 7.49(s,2H), 7.57(m,1H), 7.73(m,1H), 7.81(m,1H), 8.08(d,1H), 8.14(d,1H), 8.93(d,1H)
$HN(CH_2)_3OH$	1.85(m,2H), 2.50(s,3H), 2.68(s,3H), 3.65(t,2H), 3.85(q,2H), 6.15(brs,1H), 7.50(s,2H)
$PhCH_2N$-n-Pr	0.9(t,3H), 1.75(m,2H), 2.48(s,3H), 2.60(s,3H), 3.79(t,2H), 5.1(s,2H), 7.25-7.4(m,5H), 7.50(s,2H)
p-Cl-Ph$CH_2N(CH_2)_2COOH$	2.49(s,3H), 2.54(s,3H), 2.72(t,2H), 3.88(t,2H), 5.07(s,2H), 7.1-7.3(m,4H), 7.50(s,2H)
2-tetrahydropyranyl-$CH_2N(CH_2)_3OH$	1.2-2.0(m,8H), 2.5(s,3H), 2.6(s,3H), 3.2-4.2(m,9H), 7.5(s,2H)
(p-methylbenzyl)-(2-furanylmethyl)amino	2.28(s,3H), 2.44(s,3H), 2.50(s,3H), 4.82(s,2H), 4.90(s,2H), 6.16(m,1H), 6.24(m,1H), 7.0-7.2(m,4H), 7.28(m,1H), 7.40(s,2H)
2-thiazolyl-$CH_2N(CH_2)_3OH$	2.00(m,2H), 2.53(s,3H), 2.58(s,3H), 3.63(t,2H), 3.97(t,2H), 5.36(s,2H), 7.32(d,1H), 7.48(s,2H), 7.50(d,1H)
2-benzothiazolyl-$CH_2N(CH_2)_3OH$	2.6(s,3H), 3.67(t,2H), 4.05(t,2H), 5.5(s,2H), 7.35-7.55(m,2H), 7.5(s,2H), 7.85(d,1H), 8.05(d,1H)
p-Me-Ph$CH_2N(CH_2)_3NH_2$	1.7(brs,2H), 1.8(m,2H), 2.3(s,3H), 2.44(s,3H), 2.52(s,3H), 2.68(m,2H), 3.71(t,2H), 5.0(s,2H), 7.05-7.18(m,4H), 7.44(s,2H)

NR_1R_2	^1H NMR ($CDCl_3$) ppm
p-H_2N-$PhCH_2N(CH_2)_3OH$	1.73(m,2H), 2.50(s,3H), 2.55(s,3H), 3.55(t,2H), 3.82(t,2H), 5.0(s,2H), 6.7(d,2H), 7.05(d,2H), 7.48(s,2H)
3-benzothienyl-$CH_2N(CH_2)_3OH$	1.8(m,2H), 2.48(s,3H), 2.52(s,3H), 3.55(t,2H), 3.97(t,2H), 5.35(s,2H), 7.28(s,1H), 7.35-7.45(m,2H), 7.55(m,1H), 7.88(m,1H)
p-Me-$PhCH_2NCH_2CH(OH)CH_2OH$	2.37(s,3H), 2.51(s,3H), 2.55(s,3H), 3.4-3.6(m,3H), 3.7-4.0(m,2H), 5.17(ABq,2H), 7.20(s,4H), 7.51(s,2H)
NEt_2	1.33(t,4H), 2.46(s,3H), 2.65(s,3H), 3.82(q,4H), 7.49(s,2H)
$PhCH_2N(CH_2)_3F$	2.0-2.2(m,2H), 2.46(s,3H), 2.56(s,3H), 3.78(m,2H), 4.50(dt, J=45 & 6 Hz), 5.08(s,2H), 7.23(s,5H), 7.46(s,2H)
$PhCH_2N(CH_2)_3Cl$	2.1-2.2(m,2H), 2.47(s,3H), 2.57(s,3H), 3.57(t,2H), 3.80(t,2H), 5.08(s,2H), 7.2-7.4(m,5H), 7.48(s,2H)
n-$BuN(CH_2)_2OH$	0.96(t,3H), 1.35-1.50(m,2H), 1.7-1.8(m,2H), 2.45(s,3H), 2.64(s,3H), 3.80-3.97(m,6H), 5.71(s, 1H), 7.48(s,2H)
$EtN(CH_2)_2OH$	1.43(t,3H), 2.47(s,3H), 2.66(s,3H), 3.90-4.0(m,6H), 5.78(s,1H), 7.50(s,2H)
NMe_2	2.49(s,3H), 2.64(s,3H), 3.38(s,6H), 7.49(s,2H)
N(n-Bu)$_2$	0.97(t,6H), 1.3-1.5(m,4H), 1.65-1.82(m,4H), 2.46(s,3H), 2.64(s,3H), 3.73(t,4H), 7.49(s,2H)
$CH_3(CH_2)_4N(CH_2)_2OH$	0.90(t,3H), 1.3-1.42(m,4H), 1.68-1.82(m,2H), 2.42(s,3H), 2.61(s,3H), 3.70-3.95(m,6H), 7.46(s,2H)
$CH_3(CH_2)_4NCH_2CH_3$	0.95(t,3H), 1.30(t,3H), 2.43(s,3H), 2.61(s,3H), 3.68(t,2H), 3.76(q,2H), 7.46(s,2H)
2-pyrrolyl-$CH_2N(CH_2)_3OH$	1.86(m,2H), 2.53(s,3H), 2.62(s,3H), 3.56(m,2H), 3.84(t,2H), 4.88(s,2H), 6.14(m,1H), 6.20(m,2H), 6.76(m,1H), 7.48(s,2H), 9.22(brs,1H)

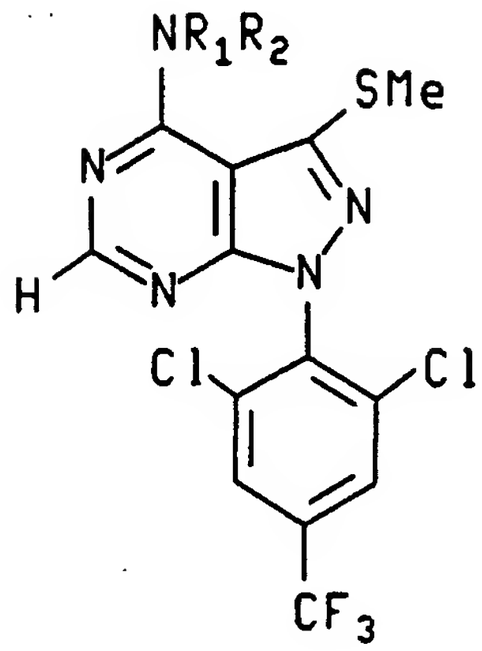
NR_1R_2	^1H NMR ($CDCl_3$) ppm
$HO(CH)_3CH_2N(CH_2)_2OH$	1.98(m,2H), 2.44(s,3H), 2.65(s,3H), 3.67(t,2H), 3.84-4.02(m,6H), 7.48(s,2H)
$HO(CH_2)_2N(CH_2)_2OH$	2.44(s,3H), 2.64(s,3H), 3.9-4.1(m,8H), 7.47(s,2H)
$EtO(CH_2)_2N(CH_2)_2OEt$	1.18(t,6H), 2.44(s,3H), 2.66(s,3H), 3.51(q,4H), 3.74(t,4H), 4.09(t,4H), 7.47(s,2H)
$EtOCO(CH_2)_2NEt$	1.26(t,2H), 1.37(t,3H), 2.47(s,3H), 2.64(s,3H), 2.80(t,2H), 3.87(q,2H), 4.01(t,2H), 4.18(q,2H), 7.50(s,2H)
n-BuN-$(CH_2)_3OH$	1.03(t,3H), 1.4-1.6(m,2H), 1.7-2.0(m,4H), 2.47(s,3H), 2.66(s,3H), 3.5-3.65(m,2H), 3.81(dd,2H), 3.95(t,2H), 4.78(brs,1H,OH), 7.50(s,2H)
n-BuNMe	0.96(t,3H), 1.38(m,2H), 1.69(m,2H), 2.45(s,3H), 2.62(s,3H), 3.36(s,3H), 3.77(t,2H), 7.47(s,2H)
$EtN(CH_2)_2COOH$	1.41(t,3H), 2.63(s,3H), 2.64(s,3H), 2.83(t,2H), 3.80-4.00(m,4H), 7.48(s,2H)
n-BuN$(CH_2)_4OH$	0.94(t,3H), 1.37(m,2H), 1.54-1.80(m,6H), 2.44(s,3H), 2.61(s,3H)
p-HO-Ph$CH_2N(CH_2)_3OH$	1.7-1.9(m,2H), 2.51(s,3H), 2.56(s,3H), 3.57(t,2H), 3.86(t,2H), 4.75(brs,1H), 5.08(s,2H), 5.95(brs,1H), 6.65(d,2H), 7.16(d,2H), 7.46(s,2H)
$H_2NCO(CH_2)_2NEt$	1.32(t,3H), 2.41(s,3H), 2.59(s,3H), 2.64(t,2H), 3.83(q,2H), 3.96(t,2H), 5.10(brs,1H), 6.40(brs,1H), 7.45(s,2H)
$EtNHCO(CH_2)_2NEt$	1.14(t,3H), 1.37(t,3H), 2.47(s,3H), 2.60(t,2H), 2.65(s,3H), 3.30(q,2H), 3.89(q,2H), 4.02(t,2H), 6.05(brs,1H), 7.50(s,2H)
Pr-N-Pr	0.98(t,6H), 1.76(m,4H), 2.46(s,3H), 2.64(s,3H), 3.71(dd,4H), 7.49(s,2H)
cyclopropyl-CH_2N-Pr	0.31(m,2H), 0.61(m,2H), 1.01(t,3H), 1.10-1.30(m,1H), 1.70-1.90(m,2H), 2.47(s,3H), 2.65(s,3H), 3.67(d,2H), 3.84(dd,2H), 7.49(s,2H)

NR_1R_2	^1H NMR ($CDCl_3$) ppm
$EtCH(CH_3)CH_2N(CH_2)_2OH$	0.92(t,6H), 1.10-1.30(m,2H), 1.40-1.55(m,2H), 1.75-1.95(m,2H), 2.48(s,3H), 2.65(s,3H), 3.88(dd,2H), 3.85-3.95(m,4H), 5.50(brs,1H), 7.51(s,2H)
CH_3CON-Bu	0.88(t,3H), 1.32(m,2H), 1.56(s,3H), 1.62(m,2H), 2.06(s,3H), 2.64(s,3H), 2.72(s,3H), 3.93(t,2H), 7.53(s,2H)
$MeO(CH_2)_2N(CH_2)_2OMe$	2.46(s,3H), 2.64(s,3H), 3.39(s,6H), 3.73(t,4H), 3.12(t,4H), 7.52(s,2H)
cyclopropyl-CH_2-N-$(CH_2)_2OH$	0.31(q,2H), 0.71(q,2H), 1.10-1.30(m,1H), 2.48(s,3H), 2.66(s,3H), 3.76(d,2H), 3.90-4.10(m,4H), 7.51(s,2H)
$Me_2N(CH_2)_2NEt$	1.38(t,3H), 2.35(s,6H), 2.46(s,3H), 2.64(s,3H), 2.60-2.70(m,2H), 3.80-3.95(m,4H), 7.51(s,2H)
$CH_2=C(CH_3)CH_2NEt$	1.28(t,3H), 1.78(s,3H), 2.47(s,3H), 2.63(s,3H), 3.79(q,2H), 4.41(s,2H), 4.94(dd,2H), 7.49(s,2H)
$CH_2=CHCH_2NCH_2CH=CH_2$	2.48(s,3H), 2.64(s,3H), 4.38(d,4H),5.25(dd,2H), 5.30(s,1H), 5.90-6.10(m,2H), 7.50(s,2H)
$CH\equiv CH_2NCH_2C\equiv CH$	2.32(t,2H), 2.52(s,3H), 2.65(s,3H), 4.67(d,4H), 7.48(s,2H)

Example 3

The following compounds were prepared starting with the appropriate amine and 4-chloro-3-methylsulfanyl-1-(2,4-dichloro-6-trifluoromethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine and employing the procedure of Example 1.

Table 2



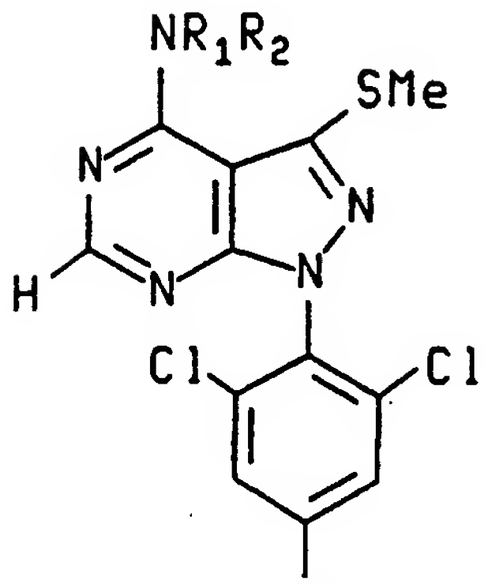
NR_1R_2	^1H NMR ($CDCl_3$) ppm
m-Me-$PhCH_2NH$	2.36(s,3H), 2.65(s,3H), 4.82(d,2H), 6.20(t,1H), 7.06-7.30(m,4H), 7.73(s,2H), 8.38(s,1H)
pyrrolidinyl	2.05(m,4H), 2.65(s,3H), 3.95(m,4H), 7.75(s,2H), 8.30(s,1H)
pyrrolyl	2.65(s,3H), 6.50(m,2H), 7.72(m,2H), 7.80(s,2H), 8.75(s,1H)
thiazolidinyl	2.66(s,3H), 3.16(t,2H), 4.25(t,2H), 7.75(s,2H), 8.35(s,1H)
$PhCH_2NEt$	1.29(t,3H), 2.60(s,3H), 3.80(q,2H), 5.09(s,2H), 7.2-7.4(m,5H), 7.75(s,2H), 8.33(s,1H)
thiomorpholinyl	2.65(s,3H), 2.85-2.95(m,4H), 4.1-4.25(m,4H), 7.75(s,2H), 8.35(s,1H)
$PhCH_2N(CH_2)_2OH$	2.55(s,3H), 3.8-3.95(m,4H), 5.40(s,2H), 7.30-7.45(m,5H), 7.75(s,2H), 8.32(s,1H)
NEt_2	1.36(t,6H), 2.67(s,3H), 3.85(q,4H), 7.76(s,2H), 8.31(s,1H)
$PhCH_2NMe$	2.62(s,3H), 3.35(s,3H), 5.08(s,2H), 7.3-7.4(m,5H), 7.75(s,2H), 8.35(s,1H)
$EtN(CH_2)_2OH$	1.45(t,3H), 2.69(s,3H), 3.9-4.05(m,6H), 7.77(s,2H), 8.27(s,1H)

NR_1R_2	^1H NMR ($CDCl_3$) ppm
$Et_2N(CH_2)_2N(CH_2)_2OH$	1.03(t,6H), 2.58(q,4H), 2.66(s,3H), 2.9-3.0(m,2H), 3.9-4.2(m,6H), 7.76(s,2H), 8.31(s,1H)
$HO(CH_2)_2N(CH_2)_2OH$	2.68(s,3H), 3.95-4.15(m,8H), 7.77(s,2H), 8.27(s,1H)
$n\text{-}BuN(CH_2)_2OH$	0.98(t,3H), 1.37-1.52(m,2H), 1.7-1.9(m,2H), 2.68(s,3H), 3.8-4.0(m,2H), 3.91(s,4H), 7.77(s,2H), 8.28(s,1H)
$p\text{-}Cl\text{-}PhCH_2N(CH_2)_2OH$	2.60(s,3H), 3.90(s,4H), 5.19(s,2H), 7.25-7.45(m,4H), 7.78(s,2H), 8.35(s,1H)
$PhCH_2N(CH_2)_3OH$	1.8-1.9(m,2H), 2.58(s,3H), 3.61(t,2H), 3.89(t,2H), 5.19(s,2H), 7.25-7.50(m,5H), 7.78(s,2H), 8.36(s,1H)
$p\text{-}Cl\text{-}PhCH_2NH$	2.71(s,3H), 4.87(d,2H), 6.27(t,1H), 7.37(s,4H), 7.77(s,2H), 8.42(s,1H)
$p\text{-}Cl\text{-}PhCH_2N(CH_2)_2CH_3$	0.95(t,3H), 1.65-1.85(m,2H), 2.65(s,3H), 3.69(dd,2H), 5.06(s,2H), 7.2-7.4(m,4H), 7.77(s,2H), 8.35(s,1H)
$p\text{-}Cl\text{-}PhCH_2N(CH_2)_3CH_3$	0.93(t,3H), 1.20-1.45(m,4H), 1.6-1.8(m,2H), 2.64(s,3H), 3.72(dd,2H), 5.06(s,2H), 7.2-7.4(m,4H), 7.77(s,2H), 8.35(s,1H)
$m\text{-}Cl\text{-}PhCH_2N(CH_2)_3OH$	1.8-1.95(m,2H), 2.57(s,3H), 3.60(m,2H), 3.9(t,2H), 5.12(s,2H), 7.15-7.35(m,4H), 7.75(s,2H), 8.35(s,1H)

Example 4

The following compounds were prepared starting with the appropriate amine and 4-chloro-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine and employing the procedure of Example 1.

Table 3



NR_1R_2	^1H NMR ($CDCl_3$) ppm
$PhCH_2N(CH_2)_2OH$	2.59(s,3H), 3.7-4.0(m,4H), 5.23(s,2H), 7.3-7.45(m,5H), 7.53(s,2H), 8.34(s,1H)
$PhCH_2N(CH_2)_3OH$	1.75-1.90(m,2H), 2.57(s,3H), 3.57(t,2H), 3.87(t,2H), 5.18(s,2H), 7.25-7.45(m,5H), 7.52(s,2H), 8.34(s,1H)
p-Cl-$PhCH_2N(CH_2)_2OH$	2.57(s,3H), 3.86(s,4H), 4.35(brs,1H), 5.16(s,2H), 7.2-7.4(m,4H), 7.51(s,2H), 8.32(s,1H)
p-Cl-$PhCH_2N(CH_2)_3OH$	1.72-1.88(m,2H), 2.52(s,3H), 3.54(t,2H), 3.80(t,2H), 5.05(s,2H) 7.1-7.35(m,4H), 7.45(s,2H), 8.25(s,1H)

Example 5

The following compounds were prepared starting with the appropriate amine and the appropriate 4-chloro-1H-pyrazolo[3,4-d]pyrimidine and employing the procedure of Example 1.

3-{benzyl-[6-ethyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propanol:

^1H NMR ($CDCl_3$): 1.25(t,3H), 1.82(m,2H), 2.52(s,3H), 2.76(q,2H), 3.58(t,2H), 3.87(t,2H), 5.15(s,2H), 7.25-7.4(m,5H), 7.50(s,2H)ppm.

3-{(p-chlorobenzyl)-[6-methyl-3-methylsulfanyl-1-(2,6-dichloro-4-trifluoromethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propanol:

^{1}H NMR ($CDCl_3$): 1.83(m,2H), 2.52(s,3H), 2.55(s,3H), 3.59(m,2H), 3.88(t,2H), 4.36(t,1H), 5.12(s,2H), 7.2-7.4(m,4H), 7.76(s,2H)ppm.

3-{benzyl-[6-methyl-3-methylsulfanyl-1-(2,6-dichloro-4-trifluoromethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propanol:

^{1}H NMR ($CDCl_3$): 1.80(m,2H), 2.50(s,3H), 2.52(s,3H), 3.55(t,2H), 3.88(t,2H), 5.15(s,2H), 7.25-7.45(m,5H), 7.75(s,2H)ppm.

3-{benzyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propanol:

^{1}H NMR ($CDCl_3$): 1.75-1.85(m,2H), 1.95(s,6H), 2.33(s,3H), 2.50(s,6H), 3.51(t,2H), 3.90(t,2H), 5.20(s,2H), 7.0(s,2H), 7.25-7.45(m,5H)ppm.

3-{benzyl-[3,6-dimethyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propanol:

^{1}H NMR ($CDCl_3$): 1.84-2.0(m,2H), 2.41(s,3H), 2.51(s,3H), 3.55(t,2H), 3.91(t,2H), 4.99(s,2H), 7.3-7.5(m,5H), 7.47(s,2H)ppm.

3-{(4-methylbenzyl)-[6-methyl-3-propyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propanol:

^{1}H NMR ($CDCl_3$): 0.78(t,3H), 1.65-1.90(m,4H), 2.38(s,3H), 2.54(s,3H), 2.77(t,2H), 3.57(t,2H), 3.89(t,2H), 4.93(s,2H), 7.18(q,4H), 7.50(s,2H)ppm.

3-{(4-methylbenzyl)-[6-methyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propanol:

^{1}H NMR ($CDCl_3$): 1.85(m,2H), 2.32(s,3H), 2.52(s,3H), 3.57(m,2H), 3.96(t,2H), 4.92(s,2H), 5.51(brs, 1H), 7.1-7.2(m,4H), 7.50(s,2H)ppm.

3-{(4-methylbenzyl)-[6-methyl-3-ethyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propanol:

^{1}H NMR ($CDCl_3$): 1.23(t,3H), 1.78(m,2H), 2.34(s,3H), 2.50(s;3H), 3.54(t,2H), 3.85(t,2H), 4.90(s,2H), 7.15(q,4H), 7.48(s,2H)ppm.

3-{(4-methylbenzyl)-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propanol:

^{1}H NMR ($CDCl_3$): 1.82(m,2H), 1.90(s,6H), 2.3(s,3H), 2.35(s,3H), 2.41(s,3H), 2.55(s,3H), 3.55(t,2H), 3.93(t,2H), 4.95(s,2H), 6.94(s,2H), 7.18(q,4H)ppm.

3-{benzyl-[6-chloro-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propanol:

^{1}H NMR ($CDCl_3$): 1.85(m,2H), 2.54(s,3H), 3.62(t,2H), 3.85(t,2H), 5.17(s,2H), 7.25-7.4(m,5H), 7.50(s,2H)ppm.

3-{benzyl-[3-methylsulfanyl-6-trifluoromethyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propanol:

^{1}H NMR ($CDCl_3$): 1.96(m,2H), 2.11(t,1H), 2.60(s,3H), 3.68(q,2H), 3.93(t,2H), 5.22(s,2H), 7.2-7.4(m,5H), 7.55(s,2H)ppm.

3-{benzyl-[3-methylsulfanyl-1-(*σ*-naphthyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propanol:

^{1}H NMR ($CDCl_3$): 2.60(s,3H), 3.8-4.0(m,4H), 5.25(s,2H), 7.25-7.70(m,10H), 7.9-8.05(m,2H), 8.30(s,1H) ppm.

2-{butyl-[6-methyl-3-methylsulfanyl-1-(2,4-dichloro-6-trifluoromethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethanol:

^{1}H NMR ($CDCl_3$): 1.0(t,3H), 1.45(m,2H), 1.77(m,2H), 3.8-4.0(m,6H), 5.62(brs,1H), 7.72(s,2H)ppm.

ethyl-butyl-[6-chloro-3-methylsulfanyl-1(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine:

^{1}H NMR ($CDCl_3$): 0.97(t,3H), 1.34(t,3H), 1.44(m,2H), 1.72(m,2H), 2.63(s,3H), 3.73(dd,2H), 3.83(q,2H), 7.47(s,2H)ppm.

butyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3.4-d]pyrimidin-4-yl]-ethyl-amine

^{1}HNMR($CDCl_3$):0.96(t,3H), 1.29(t,3H), 1.3-1.45(m,2H), 1.6-1.8(m,2H), 1.90(s,6H), 2.29(s,3H), 2.42(s,3H), 2.66(s,3H), 3.70(dd,2H), 3.77(q,2H), 6.92(s,2H) ppm.

sec-butyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[pyrazolo[3.4.-d]pyrimidin-4-yl]amine

^{1}H NMR ($CDCl_3$):1.00(t,3H), 1.3(d,3H), 1.6-1.72(m,2H), 1.90(2 sets of s,6H), 2.30(s,3H), 2.49(s,3H), 2.62(s,3H), 4.4-4.5(m,1H), 4.9(d,1H), 6.9(s,2H) ppm.

[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3.4.-d]pyrimidin-4-yl](1-ethyl-propyl)-amine hydrochloride

^{1}H NMR ($CDCl_3$):1.08(t,6H), 1.83(m,4h),1.90(s,6H), 2.35(s,3H), 2.60(s,3H), 2.75(s,3H), 4.0-4.15(m,1H), 6.97(s,2H), 10.1(d,1H), 14.9(s,1H) ppm.

2-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3.4.-d]pyrimidin-4-ylamino]-butan-1-ol hydrochloride

^{1}H NMR ($CDCl_3$):1.07(t,3H), 1.8-2.0(m,2H), 1.89(s,3H), 1.91(s,3H), 2.33(s,3H), 2.76(s,3H), 2.84(s,3H), 3.69(brs,1H), 4.03(brs,1H), 5.05(brs,1H), 6.58(brs,1H), 6.98(s,2H).

Example 6

3-{Benzyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propan-1-ol acetate.

A solution of 3-{benzyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]amino}-propanol (80 mg, 0.148 mmol) in 1 ml of methylene chloride was treated with acetic anhydrous (38 mg, 0.37 mmol) and triethyl amine (38 mg, 0.37 mmol) and stirred at room temperature for 15 hours. The mixture was quenched with water and a few drops of dilute HCl and extracted with ethyl acetate. The organic layer was neutralized with aqueous sodium bicarbonate and washed with brine, separated, dried and concentrated to give the title compound as an oil. The oil was purified through silica gel column chromatography using chloroform as eluent to give 57 mg of the title compound as a white glass form. ^{1}H NMR ($CDCl_3$): 2.0(s,3H), 2.03(m,2H), 2.45(s,3H), 2.60(s,3H), 3.74(t,2H), 4.10(t,2H), 5.1(s,2H), 7.2-7.4(m,5H), 7.50(s,2H)ppm.

Example 7

The following compounds were prepared by the acylation of the Example 6 starting from the corresponding hydroxy derivative.

3-{(4-methyl-benzyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propan-1-ol acetate:

^{1}H NMR ($CDCl_3$): 1.99(s,3H), 1.95-2.06(m,2H), 2.22(s,3H), 2.49(s,3H), 2.59(s,3H), 3.75(t,2H), 4.12(t,2H), 5.05(s,2H), 7.18(q,4H), 7.50(s,2H)ppm.

2-{ethyl-[3-methylsulfanyl-1-(2,6-dichloro-4-trifluoromethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethan-1-ol acetate:

^{1}H NMR ($CDCl_3$): 1.39(t,3H), 2.07(s,3H), 2.69(s,3H), 3.98(q,2H), 4.04(t,2H), 4.43(t,2H), 7.77(s,2H), 8.32(s,1H)ppm.

2-{butyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethan-1-ol acetate:

^{1}H NMR ($CDCl_3$): 0.98(t,3H), 1.3-1.5(m,2H), 1.65-1.85(m,2H), 2.04(s,3H), 2.47(s,3H), 2.65(s,3H), 3.83(t,2H), 4.02(t,2H), 4.40(t,2H), 7.50(s,2H)ppm.

Example 8

4-{N-(4-methyl-benzyl)-N-(3-methoxy)propyl}amino-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine.

A solution of 3-{(4-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propanol (96 mg, 0.15 mmol) in 1 ml of dry tetrahydrofuran (THF) was treated with sodium hydride (60% in oil) (7 mg, 0.18 mmol), then methyl iodide was added. The mixture was stirred at room temperature for 15 hours, then quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give a colorless form which was purified through silica gel column chromatography using chloroform as eluent to give 60 mg of the title compound as a white glass form. ^{1}H NMR ($CDCl_3$): 1.95(m,2H), 2.32(s,3H), 2.47(s,3H), 2.56(s,3H), 3.24(s,3H), 3.39(t,2H), 3.75(t,2H), 5.01(s,2H), 7.15(q,4H), 7.47(s,2H)ppm.

Example 9

The following compounds were prepared according to the procedure of the Example 8 starting with the corresponding hydroxy derivative, and alkyl iodide.

4-[benzyl-(3-ethoxypropyl)]amino-3-methylsulfanyl-6-methyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine:

^{1}H NMR ($CDCl_3$): 1.12(t,3H), 1.97(m,2H), 2.47(s,3H), 2.56(s,3H), 3.37(q,2H), 3.48(t,2H), 3.80(t,2H), 5.07(s,2H), 7.23-7.40(m,5H), 7.49(s,2H)ppm.

4-[benzyl-(3-methoxypropyl)]amino-3-methylsulfanyl-6-methyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine:

^{1}H NMR ($CDCl_3$): 2.0(m,2H), 2.5(s,3H), 2.57(s,3H), 3.25(s,3H), 3.4(t,2H), 3.8(t,2H), 5.1(s,2H), 7.2-7.4(m,5H), 7.48(s,2H)ppm.

Example 10

3-{Benzyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propan-1-ol methylcarbamate.

A solution of 3-{benzyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propan-1-ol (100 mg, 0.191 mmol) in 2 ml of dry THF was treated with 6 mg of 60% sodium hydride in oil and methyl isocyanate (39 mg,

6.78 mmol) at room temperature and stirred at room temperature for 10 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 110 mg of white form. The form was purified through silica gel column chromatography to give 79 mg of the title compound as a white glass form. ^{1}H NMR ($CDCl_3$): 2.03(m,2H), 2.51(s,3H), 2.59(s,3H), 2.77(d,3H), 3.79(t,2H), 4.12(t,2H), 4.50(brs,1H), 5.17(s,2H), 7.2-7.45(m,5H), 7.51(s,2H)ppm.

Example 11

The following compounds were prepared according to the procedure of Example 10 starting from the corresponding hydroxy derivative and methyl isocyanate or methyl thioisocyanate.

3-{(4-methyl-benzyl)-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propan-1-ol methylcarbamate:

^{1}H NMR ($CDCl_3$): 2.02(m,2H), 2.36(s,3H), 2.49(s,3H), 2.59(s,3H), 2.77(d,3H), 3.76(t,2H), 4.12(t,2H), 4.55(brs,1H), 5.12(s,2H), 7.29(q,4H), 7.50(s,2H)ppm.

4-[(p-methylbenzyl)-3-(N-methylsulfanylcarbamoyloxypropyl)]amino-3-methylsulfanyl-6-methyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine and 4-[(p-methylbenzyl)-3-(N-methylcarbamoylthiopropyl)]amino-3-methylsulfanyl-6-methyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine:

A mixture of the title compounds was obtained in a 2:1 ratio. ^{1}H NMR ($CDCl_3$): 2.05-2.25(m,2H), 2.36(s,3H), 2.51(s,3H), 2.59(s,1/3x3H), 2.60(2/3x3H), 2.75(d, 1/3x3H), 3.05(d,2/3x3H), 3.78(t,2H), 4.47(t,2/3x2H), 4.54(t,1/3x2H), 5.06(s,2H), 6.2(brs,2/3H), 6.5(brs, 1/3H), 7.19(q,4H), 7.51(s,3H)ppm.

Example 12

3-{Benzyl-[6-methyl-3-methylsulfinyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propanol.

A solution of 3-{benzyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}propanol (42 mg, 0.077 mmol) and m-chloroperbenzoic acid (14 mg, 0.081 mmol) in 0.5 ml of methylene chloride was stirred at room temperature for 3 hours. The mixture was quenched with water and saturated sodium thiosulfate, and extracted with methylene chloride. The organic layer was washed with saturated sodium bicarbonate, dried and concentrated to give an oil which was purified through silica gel column chromatography using 2% methanol in chloroform as eluent to give 46 mg of the title compound as a white glass form. ^{1}H

NMR ($CDCl_3$): 1.88(m,2H), 2.54(s,3H), 2.73(s,3H), 3.5-3.7(m,4H), 4.3(m,1H), 5.15(ABq,J_{AB}=16Hz,2H), 7.2-7.4(m,5H), 8.47(ABq,2H)ppm.

Example 13

The following compounds were prepared by the method of Example 12 starting with the corresponding methylsulfanyl derivative.

4-(n-butyl-ethyl)amino-3-methylsulfinyl-6-methyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine:

^1H NMR ($CDCl_3$): 0.98(t,3H), 1.35(t,3H), 1.46(m,2H), 1.71(m,2H), 2.48(s,3H), 3.08(s,3H), 3.65-4.10(m,4H), 7.52(ABq,J_{AB}=2Hz,2H)ppm.

4-diethylamino-3-methylsulfinyl-6-methyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine:

^1H NMR ($CDCl_3$): 1.36(t,6H), 2.49(s,3H), 3.11(s,3H), 3.78(m,2H), 3.99(m,2H), 7.52(ABq, J_{AB}=1.7Hz, 2H)ppm.

Example 14

The following compounds were prepared by the method similar to that of the Example 12 starting with the corresponding methylsulfanyl derivative and 2.5 equivalents of m-chloroperbenzoic acid in methylene chloride and stirred at room temperature for 15 hours.

3-{benzyl-[6-methyl-3-methylsulfonyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propanol:

^1H NMR ($CDCl_3$): 1.8(m,2H), 2.52(s,3H), 3.40(s,3H), 3.60(t,2H), 3.90(t,2H), 5.16(s,2H), 7.2-7.4(m,4H), 7.50(s,2H)ppm.

3-{(4-methyl-benzyl)-[6-methyl-3-methylsulfonyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propanol:

^1H NMR ($CDCl_3$): 1.8(m,2H), 2.34(s,3H), 2.52(s,3H), 3.43(s,3H), 3.61(t,2H), 3.90(t,2H), 5.14(s,2H), 7.13(s,4H), 7.56(s,2H)ppm.

4-(N-butyl-N-ethyl)amino-6-methyl-3-methylsulfonyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine:

^1H NMR ($CDCl_3$): 0.95(t,3H), 1.30(t,3H), 1.37(m,2H), 1.69(m,2H), 2.47(s,3H), 3.42(s,3H), 3.85(t,2H), 3.93(q,2H), 7.53(s,2H)ppm.

4-N,N-diethylamino-6-methyl-3-methylsulfonyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine:

^1H NMR ($CDCl_3$): 1.29(t,3H), 2.45(s,3H), 3.40(s,3H), 3.91(q,2H), 7.50(s,1H)ppm.

2-{N-butyl-N-[6-methyl-3-methylsulfonyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethanol:

^{1}H NMR ($CDCl_3$): 0.95(t,3H), 1.30-1.50(m,2H), 1.50-1.70(m,2H), 2.66(s,3H), 2.76(t,2H), 3.16(t,2H), 3.44(s,3H), 3.9-4.0(m,1H), 4.79(t,2H), 7.55(s,2H)ppm.

Example 15

Ethyl-butyl-[6-methoxy-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]amine

To 1 ml of methanol was added sodium (25 mg) and the mixture was stirred until all the sodium was dissolved completely. The resulting solution was treated with ethyl-butyl-[6-chloro-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-yl]amine (100 mg, 0.21 mmol) and heated at reflux for 3 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give an oil residue. The oil residue was purified by silica gel column chromatography to give 73 mg of the title compound as a colorless oil. ^{1}H NMR ($CDCl_3$):0.96(t,3H), 1.35(t,3H), 1.42(m,2H), 1.71(m,2H), 2.63(s,3H), 3.74(dd,2H), 3.86(q,2H), 3.91(s,3H), 7.46(s,2H)ppm.

Example 16

2-Butyl-2-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-malonic acid dimethylester

A suspension of 60% sodium hydride in oil (0.240 g, 6 mmol) in 5 ml of dimethylsulfoxide (DMSO) was treated with dimethyl butylmalonate (0.948 g, 6 mmol). After stirring for 10 minutes, 4-chloro-3-thiomethyl-6-methyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine (1.182 g, 3 mmol) was added and the resulting mixture was heated at 100°C for 1 hour. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give the crude product as an oil which was diluted with 2-propanol and concentrated to dryness to give a yellow solid. The solid was purified through silica gel column chromatography, using 60:40 of chloroform:hexane to 80:20 of chloroform:hexane as eluent, to give 1.349 g of product as a yellow solid which was triturated with methanol to give 669 mg of yellow solid, m.p. 146-152°C; ^{1}H NMR($CDCl_3$): 0.81(t,3H), 1.10-1.40(m,4H), 2.54-2.63(m,2H), 2.65(s,3H), 2.66(s,3H), 3.84(s,6H), 7.52(s,2H)ppm.

Example 17

2-Butyl-2-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-malonic acid diethylester

The title compound was prepared starting with diethyl butylmalonate and employing the procedure of Exampl 16, m.p. 148-150°C; ^{1}H NMR($CDCl_3$): 0.80(t,3H), 1.1-1.4(m,10H), 2.45-2.65(m,2H), 2.63(s,3H), 2.64(s,3H), 4.29(q, 4H), 7.50(s,2H)ppm.

Example 18

2-[6-Methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]hexanonic acid methyl ester

A solution of 2-butyl-2-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-malonic acid dimethylester (311 mg, 0.57 mmol) in 4 ml of toluene was treated with 1.5 M diisobutylaluminum hydride (DIBAL) (0.84 ml, 1.254 mmol) and stirred at room temperature for 1 hour. An additional 0.3 ml of DIBAL was added and the resulting mixture was stirred for an additional 15 minutes. The mixture was quenched with methanol and stirred for 1 hour and filtered through celite. The filtrate was concentrated to dryness. The residue was taken up with water and chloroform. The organic layer was dried and concentrated to give 290 mg of crude material which was purified through silica gel, using chloroform as eluent, to give 164 mg of the title compound as a yellow solid. ^{1}H-NMR($CDCl_3$): 0.87 (t,3H), 1.2-1.5(m,4H), 1.96-2.10(m,1H), 2.1-2.3(m,1H), 2.68(s,3H), 2.69(s,3H), 3.71(s,3H), 4.22(t,1H), 7.50(s,2H)ppm.

Example 19

2-[6-Methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl-hexanonic acid ethyl ester

The title compound was prepared by the method of Example 18 starting with 2-butyl-2-[6-methyl-3-methylsulfanyl-1-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-malonic acid diethylester. ^{1}H NMR($CDCl_3$): 0.88(t,3H), 1.20(t,3H), 1.2-1.5(m,4H), 2.0-2.1(m,1H), 2.1-2.3(m,1H), 2.67(s,3H), 2.69(s,3H), 4.19(q, 2H), 4.39(t,1H), 7.50(s,2H)ppm.

Example 20

2-Ethyl-2-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-hexanonic acid methyl ester

A solution of 2-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-hexanonic acid methyl ester (217 mg, 0.445 mmol) in 1 ml of DMSO was treated with 60% sodium hydride in oil (46 mg, 1.15 mmol). After stirring for 20 minutes at room temperature, ethyl iodide (0.2 ml) was added and the mixture was stirred at room temperature for 15 hours. The mixture was quenched with brine and extracted with ethyl acetate. The organic layer was washed twice with brine, separated, dried and concentrated to give 233 mg of the crude material which was purified through silica gel column chromatography, using methylene chloride as eluent, to give 146 mg of the title compound as an off-white solid. ^{1}H NMR($CDCl_3$): 0.74(t,3H), 0.83(t,3H), 1.2-1.4(m,2H), 2.1-2.55(m,4H), 2.64(s,3H), 2.70(s,3H, 3.74(s,3H), 7.51(s,2H)ppm.

Example 21

4-(1-Ethyl-pentyl)-6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine and 3-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-heptan-3-o]

A solution of 2-ethyl-2-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-hexanonic acid methyl ester (89 mg, 0.173 mmol) in 2 ml of dimethylformamid (DMF) was treated with lithium iodide and heated at reflux for 5 hours. An additional lithium iodide (433 mg) was added and the mixture was heated for an additional 1 hour. The mixture was neutralized with acid and extracted with ethyl acetate. The organic layer was washed with brine, dried and concentrated to give 79 mg of the crude material which contains two major components which were separated by column chromatography to give two fractions. One of the fractions showed a pure component of 3-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-heptan-3-ol and the other fraction contained a mixture of the title compounds at a weight ration of 55 to 45. ^{1}H NMR($CDCl_3$) for 3-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-heptan-3-ol: 0.68(t,3H), 0.79(t,3H), 0.8(m,1H), 1.1-1.5(m,3H), 2.0-2.2(m,2H), 2.2-2.5(m,2H), 2.67(s,3H), 2.72(s,3H), 5.79(s,1H), 7.51(s,2H)ppm. 1H NMR ($CDCl_3$) for the mixture of the title compounds: 1.4-2.4(m,10H), 1.6-1.8(m,0.55x2H), 1.8-2.0(m,0.55x2H), 2.0-

2.2(m,0.45x2H), 2.2-2.4(m,0.45x2H), 2.665(s,0.55x3H), 2.672(s,0.45x3H), 2.686(s,0.55x3H), 2.718(0.45x2H), 3.34(m,0.55H), 5.79(s,0.45H), 7.49(s,0.55 x 2H), 7.51 (s,0.45x2H)ppm.

Example 22

A. 2-(2-Ethyl-butyryl)-3-ethoxy-but-2-enenitrile

A mixture of 4-ethyl-3-oxo-hexanenitrile (1.013g, 7.28 mmol), acetic anhydride (1.5 ml) and triethyl orthoacetate (1.240 g, 7.64 mmol) was heated to reflux overnight. The reaction mixture was taken up in ethyl acetate and water. The brine and the ethyl acetate layer were separated. The organic layer was dried and concentrated to give 1.262 g of dry oil which was used directly for the next reaction. ^{1}H NMR ($CDCl_3$): 0.8-1.0(m,6H), 1.44(t,3H), 1.4-1.8(m,4H), 2.61(s,3H), 3.03(m,1H), 4.28(q, 2H)ppm.

B. 1-[5-amino-3-methyl-1-(2,4,6-trimethylphenyl)-1H-pyrazol-4-yl]-2-ethyl-butan-1-one

A mixture of 2-(2-ethyl-butyryl)-3-ethoxy-but-2-enenitrile (407 mg, 1.94 mmol) and trimethylphenylhydrazine (280 mg, 1.86 mmol) in 5 ml of methanol was heated at reflux for 5 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 584 mg of brown oil. The brown oil was purified through silica gel column chromatography, using 1: 1 of hexane: chloroform as eluent, to give 222 mg of yellow solid. 1H NMR (CDCl3): 0.8-1.0(two sets of t,6H), 1.4-1.9(m,4H), 2.04(s,6H), 2.22(s,3H), 2.32(s,3H), 2.54(s,3H), 2.85-3.05(m,1H), 5.71(brs,2H), 6.97(s,2H)ppm.

C. 4-(1-ethyl-propyl)-6-methyl-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine

A mixture of 1-[5-amino-3-methyl-1-(2,4,6-trimethylphenyl)-1H-pyrazol-4-yl]2-ethyl-butan-1-one (598 mg, 1.91 mmol), acetamide (2.311 g, 39.1 mmol) and ammonium chloride (2.057 g, 38.5 mmol) was heated at reflux of 5 hours. An additional 2.029 g of acetamide was added and the mixture was heated for an additional 16 hours (tlc showed some starting material left). An additional 2.049 g of acetamide was added and the mixture was heated an additional 6 hours and GC-MS showed that the reaction was finished. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to dryness to give a brown oil. The brown oil was purified through silica gel column chromatograph to give 221 mg of the title compound as an oil. 1H NMR (CDCl3): 0.86(t,6H), 1.70-1.85(m,2H), 1.91(s,6H), 1.90-2.05(m,2H), 2,34(s,3H), 2.70(s,3H), 2.74(s,3H)3.15-3.30(m,1H), 6.98(s,2H)ppm.

Example 23

4-(1-methoxymethyl-propoxy)-3.6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine

A mixture of 1-methoxy-2 butanol (208 mg, 1.99 mmol) and sodium hydride (53 mg, 1.33 mmol) in dry THF (1 ml) was stirred at room temperature for 10 minutes. The mixture was treated with 4-chloro-3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazoloro[3,4-d]pyrimidine (200 mg, 0.665 mmol) and stirred at room temperature for 2 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give an oil which was purified through silica gel column chromatography using chloroform as eluent to give 185 mg of the title compound as an off-white solid. 1H NMR (CDCl3): 1.02 (9t,3H), 1.7-1.9(m,2H), 1.90(s,3H), 1.91(s,3H), 2.30(s,3H), 2.53(s,3H), 2.62(s,3H), 3.41(s,3H)(, 3.5-3.89(m,2H), 5.64(m,1H), 6.94(s,2H) ppm.

Example 24

A. 2-(2-Ethyl-hexanoyl)-3-methoxy-but-2-enentrile

The title compound was prepared by the method of Example 22A starting with 4-ethyl-3-oxo-octanenitrile, acetic anhydride and trimethyl orthoacetate to give a brown oil which was purified through silica gel to give a light brown oil as a mixture of two isomers. ^{1}H NMR ($CDCl_3$): 0.8-0.95(m,6H), 1.1-1.8(m,8H), 2.62(2 sets of s,3H), 3.0-3.2(m,1H), 4.0(two sets of s)ppm.

B. 1-[5-amino-3-methyl-1-(2,4,6-trimethylphenyl)-1H-pyrazol-4-yl]2-ethyl-hexan-1-one

The title compound was prepared by the method of Example 22B starting with 2-(2-ethyl-hexanoyl)-3-methoxy-but-2-eneitrile and trimethylphenylhydrazine, as a yellow oil. 1H NMR ($CDCl_3$):0.85-1.0(m,6H), 1.20-1.40(m,4H), 1.40-1.70(m,2H), 1.70-1.85(m,2H), 2.026(s,3H),2.033(s,3H), 2.32(s,3H), 2.51(s,3H), 2.98-3.05(m,1H), 5.67(s,2H), 6.96(s,2H)ppm.

C. 4-(1-ethyl-pentyl)-6-methyl-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine

The title compound was prepared by the method of Example 22C starting with 1-[5-amino-3-methyl-1-(2,4,6-trimethylphenyl)-1H-pyrazol-4-yl]2-ethyl-hexan-1-one and acetamide to give the title compound as a clear oil. 1H NMR ($CDCl_3$): 0.86(t,6H), 1.2-1.4(m, 4H), 1.7-1.9(m,2H), 1.9-2.0(m,2H), 1.91(s,3H), 1.93(s,3H), 2.35(s,3H), 2.70(s,3H),2.74(s,3H), 3.24-3.35(m,1H), 6.99(s,2H)ppm.

The following Preparations illustrate the preparation of the starting materials used in the above Examples.

Preparation A

5-Amino-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carboxamide:

A mixture of bis(methythio)methylenecyanoacetamide (7.800 g, 50 mmol) and 2,4,6-trichlorophenylhydrazine (10.575 g, 50 mmol) in 250 ml of methanol was heated at reflux for 2.5 hours. The mixture was cooled and water was added. Precipitate formed and filtered to give 14.323 g (81.5% yield) of the title compound as a white solid. ^1H NMR($CDCl_3$): 2.6 (s,3H), 5.5(brs, 2H), 7.5(s,2H) ppm. Recrystallization of a small portion of the solid from chloroform gave white crystals; m. p. 198-199°C. Anal. Calc. for $C_{11}H_9Cl_3N_4OS$: C, 37.57; H, 2.58; N, 15.93; Found: C, 37.54; H, 2.51; N, 15.73.

Preparation B

1. 5-Amino-3-methylsulfanyl-1-(2,6-dichloro-4-trifluoromethylphenyl)-1H-pyrazole-4-carboxamide

The title compound was prepared as a white solid by the procedure of Preparation A starting with 2,6-dichloro-4-trifluoromethylphenylhydrazine. ^1H NMR ($CDCl_3$): 2.58(s,3H), 5.25(brs,2H), 7.72(s,2H)ppm.

2. 5-amino-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-1H-pyrazole-4-carboxamide.

The title compound was prepared as a white solid by the procedure of Preparation A starting from 2,4,6-trimethylphenylhydrazine. ^1H NMR ($CDCl_3$): 1.98 (s,6H), 2.25(s,3H), 2.5(s,3H), 5.2(brs,2H), 7.9(s,2H) ppm.

3. 5-amino-3-methylsulfanyl-1-(2,6-dichloro-4-trifluoromethylphenyl)-1H-pyrazole-4-carbonitrile

The title compound was prepared by the procedure of Preparation A starting with bis(methylsulfanyl)methylenemalononitrile and 2,6-dichloro-4-trifluoromethylphenylhydrazine. ^1H NMR ($CDCl_3$): 2.5(s,3H), 4.5(s,2H), 7.75(s,2H)ppm.

4. 5-amino-1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carbonitrile

The title compound was prepared as an orange solid, m.p. 208.5-209.5°C by the procedure of Preparation A starting with ethoxymethylenemalononitrile and 2,4,6-trichlorophenylhydrazine.

^1H NMR ($CDCl_3$): 4.5(brs,2H), 7.5(s,2H), 7.7(s,1H)ppm.

Preparation C

5-Amino-3-methylsulfanyl-1-(2,6-dichloro-4-trifluoromethylphenyl)-1H-pyrazole-4-carboxamide.

A mixture of 5-amino-3-methylsulfanyl-1-(2,6-dichloro-4-trifluoromethylphenyl)-1H-pyrazole-4-carbonitrile (2.7 g, 7.35 mmol), 30% hydrogen peroxide (10 ml), ammonium hydroxide (90 ml), methanol (70 ml) and water (15 ml) was stirred in a pressure reactor for 10 hours. The mixture was filtered and washed with water to give an off-white solid. The filtrate was diluted with water and extracted with ethyl acetate. The organic layer was dried and concentrated to recover more product as an off-white solid. Both portions of off-white solid were combined to give 1.400 g of the desired title compound which was identical to the first title compound of Preparation B.

Preparation D

5-Amino-1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carboxamide.

To a cooled concentrated sulfuric acid (10 ml) was added portionwise 5-amino-1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carbonitrile (4.000 g, 13.9 mmol) over a period of 45 minutes. The reaction mixture was allowed to stir at room temperature for 1 hour after addition. The mixture was poured over ice with stirring and the solution was neutralized with 15% NaOH in ice-bath. Precipitate formed and was filtered to give 3.57 g of yellow solid. ^{1}H NMR ($CDCl_3$): 5.3(brs,2H), 5.6(brs,2H), 7.5(s,2H), 7.7(s,1H)ppm.

Preparation E

2-Cyano-3-(N'-2,4,6-trichlorophenylhydrazino)but-2-enoic acid amide.

A mixture of 2-cyano-3-ethoxy-but-2-enoic acid amide (616 mg, 4 mmol) and trichlorophenylhydrazine (730 mg, 4 mmol) in 15 ml of ethanol and 3 ml of chloroform was heated at reflux for 6 hours to give 754 mg of the title compound as a white solid, m.p. 204-206°C. ^{1}H NMR (DMSO-d6): 2.35(s,3H), 6.95(brs,2H), 7.6(s,2H), 7.95(s,1H), 11.7(s,1H)ppm.

Preparation F

2-Cyano-3-(N'-2,4,6-trichlorophenylhydrazino)pent-2-enoic acid amide.

The title compound was prepared as a yellow solid by the procedure analogous to Preparation E starting from 2-cyano-3-methoxy-pent-2-enoic acid amide. ^{1}H NMR ($CDCl_3$): 1.2(t,3H), 3.0(q,2H), 4.0(s,3H), 5.5(brs,1H), 6.0(brs,1H)ppm.

Preparation G

3,6-Dimethyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-ol.

A mixture of 2-cyano-3-(N'-2,4,6-trichlorophenylhydrazino)but-2-enoic acid amide (0.620 g, 2.02 mmol) and acetamide (1 g, 16.95 mmol) was heated at reflux for 15 hours. The mixture was cooled and diluted with water and extracted with chloroform. The organic layer was separated dried and concentrated to give 0.325 g (47%) of the title compound as a brown solid. ^1H NMR ($CDCl_3$): 2.5(s,3H), 2.7(s,3H), 7.5(s,2H) ppm.

Preparation H

3-Ethyl-6-methyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-ol.

The crude material of the title compound was prepared as a brown solid by the procedure analogous to Preparation G and was used directly for the next step without purification.

Preparation I

2-Cyano-3-(N'-2,4,6-trichlorophenylhydrazino)hex-2-enoic acid amide.

The title compound was prepared as a yellow solid by the procedure analogous to Preparation E starting from 2-cyano-3-methoxy-hex-2-enoic acid. ^1H NMR ($CDCl_3$): 1.07(t,3H), 1.71(m,2H), 2.87(dd,2H), 6.19(s,1H), 7.29(s,2H), 11.50(s,1H)ppm.

Preparation J

5-Amino-3-n-propyl-1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carboxamide.

A solution of 2-cyano-3-(N'-2,4,6-trichlorophenylhydrazino)-hex-2-enoic acid amide (1.920 g, 5.552 mmol) and acetamide (3.262 g, 55.20 mmol) was heated at reflux for 3 hours. The reaction mixture was cooled and treated with 20 ml of water. Precipitate formed and was filtered to give 2.024 g of a beige solid. The solid was dissolved in ethyl acetate and water. The organic layer was separated, dried and concentrated to give 1.685 g of the title compound. ^1H NMR ($CDCl_3$): 1.02(t,3H), 1.82(m,2H), 2.75(t,2H), 5.4(brs, 1H), 5.55(brs, 1H), 7.5(s,2H)ppm.

Preparation K

3-n-Propyl-6-methyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-ol.

The title compound of Preparation J (1.617 g, 4.85 mmol) and acetamide (3.203 g, 5.42 mmol) were heated at reflux for 5 hours. Liquid chromatography (tlc) indicated that all the starting material was consumed. The mixture was cooled and quenched with water. Precipitate formed and was filtered to give a beige solid. The solid was

dissolved in chloroform and water. The organic layer was separated, dried and concentrated to give 1.617 g of brown oil of the title compound. ^{1}H NMR ($CDCl_3$): 0.95(t,3H), 1.84(m,2H), 2.44(s,3H), 2.95(t, 2H), 7.48(s, 2H), 11.15(brs,1H)ppm.

Preparation L

5-Amino-1-napthtyl-3-methylsulfanyl-1H-pyrazole-4-carboxamide.

The title compound was prepared as a yellow solid by the procedure of Preparation A starting with bis(methylsulfanyl)methylenecyanoacetamide and naphthylhydrazine. ^{1}H NMR ($CDCl_3$): 2.6(s,3H), 4.0(s,1H), 5.3(brs,1H), 5.45(brs, 1H), 7.45-7.6(m,5H), 7.9-8.05(m,2H)ppm.

Preparation M

3,6-Dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-ol.

A mixture of 2-cyano-3-ethoxy-but-2-enoic acid amide (573 mg, 3.72 mmol), 2,4,6-trimethylphenylhydrazine HCl salt (695 mg, 3.72 mmol), triethylamine (377 mg, 3.73 mmol) in 5 ml of methanol was heated at reflux for 15 hours. The reaction mixture was cooled and diluted with water, extracted with ethyl acetate. The organic layer was dried and concentrated to give 434 mg of brown solid which was used directly for the next reaction. The brown solid was treated with acetamide (1.600 g, 27 mmol) and heated at reflux for 15 hours. The reaction mixture was cooled, diluted with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 400 mg of dark-reddish solid which was purified through silica gel column chromatography using chloroform as eluent to give 110 mg of tan solid of the title compound. ^{1}H NMR ($CDCl_3$): 2.0(s,3H), 2.3(s,3H), 2.45(s,3H), 2.65(s,3H), 7.0(s,2H)ppm.

Preparation N

6-Methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-ol.

A mixture of 5-amino-1-(2,4,6-trichlorophenyl)-3-methylthiopyrazole-4-carboxamide (7.032 g, 20 mmol) and acetamide (8.850 g, 150 mmol) was heated at reflux for 15 hours. The mixture was cooled and quenched with water and a small amount of methanol. Precipitate formed and was filtered to give 4.343 g (58%) of a brown solid of the title compound. ^{1}H NMR ($CDCl_3$): 2.5(s,3H), 2.65(s,3H), 7.5(s,2H), 12.2(brs,1H)ppm.

Preparation O

6-Methyl-3-methylsulfanyl-1-(2,6-dichloro-4-trifluoromethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-ol.

The title compound was prepared in 66% yield as a yellow solid by the method analogous to that in Preparation N. ^1H NMR ($CDCl_3$): 2.5(s,3H), 2.65(s,3H), 7.75(s,2H), 11.5(brs,1H)ppm.

Preparation P

6-Methyl-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-ol.

A mixture of 5-amino-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-4-carboxamide (340 mg, 1.17 mmol) and acetamide (691 mg, 11.7 mmol) was heated at reflux for 9 hours. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give the title compound as a brown solid in 74% yield. ^1H NMR ($CDCl_3$): 2.0(s,6H), 2.3(s,3H), 2.5(s,3H), 2.6(s,3H), 7.0(s,2H), 11.7(brs,1H)ppm.

Preparation Q

6-Methyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-ol was prepared as a tan solid in 91% yield by the method of Preparation P starting with 5-amino-1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carboxamide. ^1H NMR ($CDCl_3$): 2.5(s,3H), 7.5(s,2H), 8.3(s,1H)ppm.

3-Methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-olwas prepared as a yellow solid in 75% yield by the method of Preparation P starting with 5-amino-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carboxamide and formamide. ^1H NMR ($CDCl_3$): 2.65(s,3H), 7.55 and 7.60(2 sets of s,2H), 7.8(s,0.5H), 8.15 and 8.25(2 sets of s,1H) 12.0(brs,0.5H)ppm.

3-Methylsulfanyl-1-(2,6-dichloro-4-trifluoromethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-ol was prepared as a white solid in 83% yield by the method of Preparation P starting with 5-amino-3-methylsulfanyl-1-(2,4-dichloro-6-trifluoromethylphenyl)-1H-pyrazole-4-carboxamide and formamide. ^1H NMR ($CDCl_3$): 2.6(s,3H), 7.72(s,2H), 8.0(s,1H), 12.1(brs,1H)ppm.

3-Methylsulfanyl-1-(α-naphthyl)-1H-pyrazolo[3,4-d]pyrimidine-4-ol was prepared as a brown solid in 64% yield by the method of Preparation P starting

with 5-amino-3-methylsulfanyl-1-(α-naphthyl)-1H-pyrazole-4-carboxamide and formamide. ^{1}H NMR ($CDCl_3$): 2.7(s,3H), 7.2-7.7(m,5H), 7.7-8.1(m,3H)ppm.

3-Methylsulfanyl-6-trifluoromethyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-ol was prepared as a white solid, m.p. 220-229°C, in 61% yield by the method of Preparation P starting with 5-amino-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carboxamide and trifluoroacetamide. ^{1}H NMR ($CDCl_3$): 2.6(s,3H), 7.5(s,2H)ppm.

Preparation R

4-Chloro-6-ethyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine

A mixture of 5-amino-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazole-4-carboxamide (1.0 g, 2.84 mmol) and propionamide (2.100 g, 28.77 mmol) was heated at 200°C for 15 hours. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried and concentrated to give 600 mg of a crude material which contains the desired product as well as an unidentified compound. The crude material was treated with 1.5 ml of phosphorous oxychloride and heated at reflux for 3 hours. The reaction mixture was cooled and poured over ice-water and stirred. Precipitate formed and was filtered to give 712 mg of the title compound as a brown solid. ^{1}H NMR ($CDCl_3$): 1.3(t,3H), 2.7(s,3H), 3.0(q,2H), 7.5(s,2H)ppm.

Preparation S

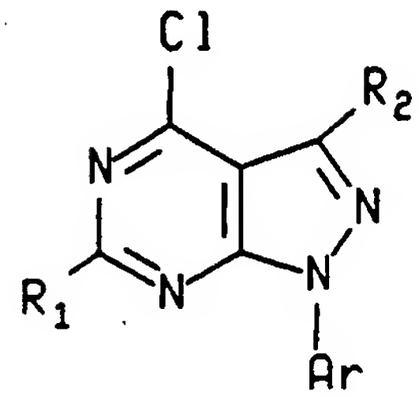
4-Chloro-3-methylsulfanyl-6-methyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine

A mixture of 3-methylsulfanyl-6-methyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidine-4-ol (3.700 g, 9.85 mmol) and phosphorous oxychloride (18.115g, 11ml) was heated at reflux for 4 hours. The mixture was cooled and poured over ice-water and stirred for 10 minutes. Precipitate formed and was filtered to give a brown solid. The brown solid was pumped in vacuo to give 3.718 g (96% yield). ^{1}H NMR ($CDCl_3$): 2.65(s,3H), 2.7(s,3H), 7.5(s,2H)ppm.

Preparation T

The procedure of Preparation S when starting with the appropriate 1H-pyrazolo[3,4-d]pyrimidine-4-ol gave the corresponding 4-chloro-pyrazolo[3,4-d]pyrimidine in Table 5..

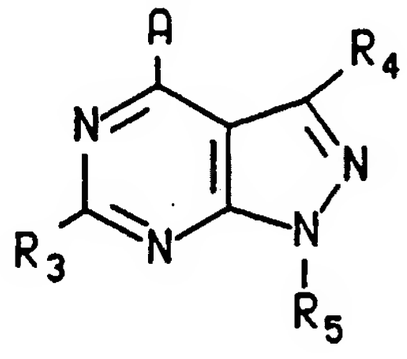
Table 5



R_1	R_2	Ar	^1H NMR ($CDCl_3$) (ppm)
Me	SMe	2,6-dichloro-4-trifluoromethylphenyl	2.65(s,3H), 2.7(s,3H), 7.75(s,2H)
Me	SMe	2,4,6-trimethylphenyl	1.95(s,6H), 2.35(s,3H), 2.65(s,3H), 2.70(s,3H), 7.0(s,2H)
Me	H	2,4,6-trichlorophenyl	2.75(s,3H), 7.55(s,2H), 8.35(s,1H)
Me	Me	2,4,6-trichlorophenyl	2.45(s,3H), 2.65(s,3H), 7.5(s,2H)
Me	Me	2,4,6-trimethylphenyl	1.90(s,6H), 2.35(s,3H), 2.75(s,3H), 2.80(s,3H), 7.0(s,2H)
Me	Et	2,4,6-trichlorophenyl	1.42(t,3H), 2.71(s,3H), 3.16(q,2H), 7.51(s,2H)
Me	n-Pr	2,4,6-trichlorophenyl	1.00(t,3H), 1.87(q,2H), 2.72(s,3H), 3.10(t,2H), 7.50(s,2H)
H	SMe	2,4,6-trichlorophenyl	2.68(s,3H) 7.78(s,2H), 8.71(s,1H)
H	SMe	2,6-dichloro-4-trifluoromethylphenyl	2.64(s,3H), 7.72(s,2H), 8.64(s,1H)
CF_3	SMe	2,4,6-trichlorophenyl	2.68(s,3H), 7.50(s,2H)

CLAIMS

1. A compound of the formula



I

and the pharmaceutically acceptable acid addition salts thereof, wherein

A is NR_1R_2, $CR_1R_2R_{11}$, or $C(=CR_1R_{12})R_2$, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$ or $C(O)R_2$;

R_1 is hydrogen, or C_1-C_6 alkyl which may be substituted by one or two substituents R_8 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_8 alkoxy, O-C-(C_1-C_8 alkyl), O-C-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), amino, NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)(C_1-C_4 alkyl), S(C_1-C_8 alkyl), OC(O)NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)C(O)(C_1-C_4 alkyl), NHC(C_1-C_4 alkyl), COOH, CO(C_1-C_4 alkyl), CNH(C_1-C_4 alkyl), CN(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and said C_1-C_6 alkyl may contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl, aryl or (C_1-C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_8 alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl, wherein R^2 may be substituted independently by from

one to three of chloro, fluoro, or C_1-C_4 alkyl, or one of hydroxy, bromo, iodo, C_1-C_6 alkoxy, O-C(=O)-(C_1-C_6 alkyl), O-C(=O)-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_6 alkyl), NH_2, NH(C_1-C_2 alkyl), N(C_1-C_2 alkyl) (C_1-C_4 alkyl), N(C_1-C_4 alkyl)-C(=O)(C_1-C_4 alkyl), NHC(=O)(C_1-C_4 alkyl), COOH, CO(C_1-C_4 alkyl), CNH(C_1-C_4 alkyl), CN(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein said C_1-C_{12} alkyl or C_1-C_{10} alkylene may contain one to three double or triple bonds; or

NR_1R_2 or $CR_1R_2R_{11}$ may form a 4- to 8-membered ring optionally containing one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl, or C_1-C_4 alkanoyl;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, O(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, S(C_1-C_4 alkyl), SO(C_1-C_4 alkyl), or SO_2(C_1-C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may contain one or two double or triple bonds and may be substituted by from 1 to 3 substituents R_7 independently selected from the group consisting of hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, diethylamino, methylamino, ethylamino, NHC(=O)CH_3, fluoro, chloro or C_1-C_3 thioalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, amino, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl) (C_1-C_2 alkyl), SO_n(C_1-C_6 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said C_1-C_6 alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido, NHC(=O)(C_1-C_4 alkyl), NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), C(=O)O(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_5 is phenyl; naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, piperazinyl, piperidinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or benzyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, formyl, C_1-C_6 alkyl, C_1-C_6 alkoxy or trifluoromethyl, or one of hydroxy, iodo, cyano, nitro, amino, cyclopropyl, $NH(C_1$-C_4 alkyl), $N(C_1$-C_4 alkyl)$(C_1$-C_2 alkyl), $COO(C_1$-C_4 alkyl), $CO(C_1$-C_4 alkyl), $SO_2NH(C_1$-C_4 alkyl), $SO_2N(C_1$-C_4 alkyl)$(C_1$-C_2 alkyl), SO_2NH_2, $NHSO_2(C_1$-C_4 alkyl), $S(C_1$-C_6 alkyl), $SO_2(C_1$-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may have one double or triple bond and may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that R_5 is not unsubstituted phenyl;

R_{11} is hydrogen, hydroxy, fluoro, chloro, $COO(C_1$-C_2 alkyl), cyano, or $CO(C_1$-C_2 aklyl); and

R_{12} is hydrogen or C_1-C_4 alkyl;

(a) A is not straight chain C_1-C_{12} alkyl;

(b) R_5 is not a sugar group;

(c) when R_3 and R_4 are hydrogen and R_5 is chlorophenyl, then A is not NH-$CH(CH_3)$-$(CH_2)_3$-$N(C_2H_5)_2$;

(d) when R_3 and R_4 are hydrogen and A is NR_1R_2 wherein R_1 is C_3-C_7 cycloalkyl, and R_2 is C_2-C_6 alkenyl, phenyl-(C_1-C_6 alkylene) or hetero-(C_1-C_6 alkylene) wherein the hetero radical is furyl, thienyl or pyridinyl, and wherein said phenyl may be substituted by fluoro, chloro, bromo or iodo, then R_5 is not tetrahydrofuranyl or tetrahydropyranyl;

(e) when R_3 is methoxy, methylthio, or methylsulfonyl, R_4 is hydrogen, and R_5 is tetrahydrofuranyl or tetrahydropyranyl, then A is not $NH(C_1$-C_2alkyl), morpholinyl, hydrazino, or $NHC_2H_4C_6H_5$ which may be substituted by one methyl or two methoxy;

(f) when R_3 is hydrogen, C_1-C_6 alkyl, hydrazino, chloro, bromo, SH, or S (C_1-C_4 alkyl), R_4 is hydrogen and R_5 is C_3-C_8 cycloalkyl, then A is not hydrazino, $NH(C_1$-C_2 alkyl) or $N(C_1$-C_6 alkyl) (C_1-C_{12} alkyl);

(g) when R_3 and R_4 are hydrogen and A is $NH(CH_2)_m$ COOH wherein m is 1-12, then R_5 is not phenyl substituted by one of fluoro, chloro, bromo or iodo;

(h) when R_3 is hydrogen, hydroxy, methylthio, chloro or NHbenzyl, R_4 is hydrogen, and R_5 is chlorophenyl or bromophenyl, then A is not $NH(C_1\text{-}C_{12}$ alkyl), NHallyl, or $N(C_1\text{-}C_6$ alkyl) $(C_1\text{-}C_{12}$ alkyl), wherein said $C_1\text{-}C_{12}$ alkyl may be substituted by NC_2H_5, or NH benzyl which may be substituted by one or two bromo, chloro, fluoro, NC_2H_5 phenyl or morpholinopropyl;

(i) when R_3 and R_4 are hydrogen and R_5 is nitrophenyl, then A is not NHR_2 wherein R_2 is $C_1\text{-}C_{12}$ alkyl which may be substituted by two hydroxy, or R_2 is phenyl or benzyl;

(j) when R_3 is chloro or $O(C_1\text{-}C_6$ alkyl), R_4 is hydrogen, and A is NR_1R_2 wherein R_1 and R_2 are independently hydrogen or $C_1\text{-}C_6$ alkyl, then R_5 is not chlorophenyl; and

(k) when R_3 is hydrogen, A is benzyl or phenethyl, and R_4 is fluoro, chloro, bromo or iodo, then R_5 is not 5'-deoxy-ribofuranosyl or 5'-amino-5'-deoxy-ribofuranosyl.

2. A compound according to claim 1 wherein R_1 is $C_1\text{-}C_4$ alkyl, $(C_2\text{-}C_4$ alkylene) $O(C_1\text{-}C_4$alkyl), or $C_2\text{-}C_4$ hydroxyalkyl.

3. A compound according to claim 1 or 2 wherein R_2 is $C_1\text{-}C_5$ alkyl.

4. A compound according to claim 1 or 2 wherein R_2 is $(C_1\text{-}C_4$ alkylene)aryl wherein said aryl is phenyl, thienyl, benzofuranyl, furanyl, benzothienyl, thiazolyl, pyridyl or benzothiazolyl.

5. A compound according to claim 1 or 2 wherein R_2 is benzyl, phenylethyl, p-fluorobenzyl, p-chlorobenzyl, p-nitrobenzyl, p-methylbenzyl, p-methoxybenzyl, p-trifluoromethylbenzyl, p-(t-butyl)benzyl, p-ethylbenzyl, (2-thienyl)methyl, (2-thienyl)ethyl, (2-furanyl)methyl, 2-(4-chlorothienyl)methyl, (2-benzofuranyl)methyl, (2-benzothienyl)methyl, (2-thiazolyl)methyl, or (2-benzothiazolyl) methyl.

6. A compound according to any one of claims 1 to 5 wherein R_3 is methyl, ethyl, methoxy, fluoro or chloro.

7. A compound according to any one of claims 1 to 6 wherein R_4 is methylthio, methylsulfinyl, methylsulfonyl, hydrogen, methyl, ethyl or n-propyl.

8. A compound according to any one of claims 1 to 7 wherein R_5 is phenyl substituted by two or three substituents.

9. A compound according to claim 8 wherein said substituent is independently fluoro, chloro, bromo, iodo, C_1-C_4 alkoxy, trifluoromethyl, C_1-C_6 alkyl which may be substituted by one of hydroxy, C_1-C_4 alkoxy or fluoro and may have one double or triple bond, -(C_1-C_4 alkylene)O(C_1-C_2 alkyl), C_1-C_3 hydroxyalkyl, hydroxy, formyl, COO(C_1-C_2 alkyl), -(C_1-C_2 alkylene)amino, or -C(O)(C_1-C_4 alkyl).

10. A compound according to claim 1 wherein said compound is

3-{(4-methyl-benzyl)-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-propan-1-ol;

diethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

2-{butyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amino}-ethanol;

dibutyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl}-amine;

butyl-ethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-ethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-cyclopropylmethyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

di-1-propyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

diallyl-[6-methyl-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

butyl-ethyl-[6-chloro-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

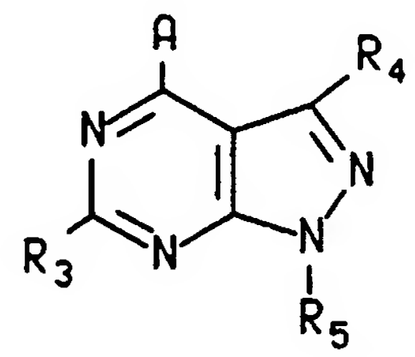
butyl-ethyl-[6-methoxy-3-methylsulfanyl-1-(2,4,6-trichlorophenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine;

propyl-ethyl-[3,6-dimethyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidin-4-yl]-amine; and

4-(1-ethyl-propyl)-6-methyl-3-methylsulfanyl-1-(2,4,6-trimethylphenyl)-1H-pyrazolo[3,4-d]pyrimidine.

11. A pharmaceutical composition for the treatment of (a) illnesses induced or facilitated by corticotropin releasing factor or (b) inflammatory disorders such as arthritis, asthma and allergies; anxiety; depression; fatigue syndrome; headache; pain; cancer; irritable bowel syndrome, including Crohn's disease, spastic colon and irritable colon; immune dysfunction; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease; gastrointestinal diseases; eating disorders such as anorexia nervosa; hemorrhagic stress; drug and alcohol withdrawal symptoms; drug addiction; stress-induced psychotic episodes; and fertility problems, which comprises a compound of the formula I as defined in claim 1 in an amount effective in the treatment of said illnesses, and a pharmaceutically acceptable carrier.

12. A method for the treatment of illnesses (a) induced or facilitated by corticotropin releasing factor or (b) inflammatory disorders such as arthritis, asthma and allergies; anxiety; depression; fatigue syndrome; headache; pain; cancer; irritable bowel syndrome, including Crohn's disease, spastic colon and irritable colon; immune dysfunction; human immunodeficiency virus (HIV) infections; neurodegenerative diseases such as Alzheimer's disease; gastrointestinal diseases; eating disorders such as anorexia nervosa; hemorrhagic stress; drug and alcohol withdrawal symptoms; drug addiction; stress-induced psychotic episodes; and fertility problems, which comprises administering to a subject in need of said treatment an amount of a compound of claim which is effective in said treatment, said compound having the formula



I

and the pharmaceutically acceptable acid addition salts thereof, wherein

A is NR_1R_2, $CR_1R_2R_{11}$, or $C(=CR_1R_{12})R_2$, $NHCR_1R_2R_{11}$, $OCR_1R_2R_{11}$, $SCR_1R_2R_{11}$, $NHNR_1R_2$, $CR_2R_{11}NHR_1$, $CR_2R_{11}OR_1$, $CR_2R_{11}SR_1$ or $C(O)R_2$;

R_1 is hydrogen, or C_1-C_6 alkyl which may be substituted by one or two substituents R_8 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, O-C-(C_1-C_6 alkyl), O-C-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), amino, NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)(C_1-C_4 alkyl), S(C_1-C_6 alkyl), OC(O)NH(C_1-C_4 alkyl), N(C_1-C_2 alkyl)C(O)(C_1-C_4 alkyl), NHC(C_1-C_4 alkyl), COOH, CO(C_1-C_4 alkyl), CNH(C_1-C_4 alkyl), CN(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and said C_1-C_6 alkyl may contain one or two double or triple bonds;

R^2 is C_1-C_{12} alkyl, aryl or (C_1-C_{10} alkylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, azaindolyl, oxazolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or (C_1-C_6 alkylene) cycloalkyl, wherein said cycloalkyl may contain one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl or C_1-C_4 alkanoyl, wherein R^2 may be substituted independently by from one to three of chloro, fluoro, or C_1-C_4 alkyl, or one of hydroxy, bromo, iodo, C_1-C_6 alkoxy, O-C-(C_1-C_6 alkyl), O-C-N(C_1-C_4 alkyl)(C_1-C_2 alkyl), S(C_1-C_6 alkyl), NH_2, NH(C_1-C_2 alkyl), N(C_1-C_2 alkyl) (C_1-C_4 alkyl), N(C_1-C_4 alkyl)-C(C_1-C_4 alkyl), NHC(C_1-C_4 alkyl), COOH, CO(C_1-C_4 alkyl), CNH(C_1-C_4 alkyl), CN(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, CN, NO_2, SO(C_1-C_4 alkyl), SO_2(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), and wherein said C_1-C_{12} alkyl or C_1-C_{10} alkylene may contain one to three double or triple bonds; or

NR_1R_2 or $CR_1R_2R_{11}$ may form a 4- to 8-membered ring optionally containing one or two double bonds or one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, benzyl, or C_1-C_4 alkanoyl;

R_3 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, hydroxy, amino, O(C_1-C_6 alkyl), NH(C_1-C_6 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SH, S(C_1-C_4 alkyl), SO(C_1-C_4 alkyl), or SO_2(C_1-C_4 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6 alkyl may contain one or two double or triple bonds and may be substituted by from 1 to 3 substituents R_7 independently selected from the group consisting of hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, diethylamino, methylamino, ethylamino, $NHC(=O)CH_3$, fluoro, chloro or C_1-C_3 thioalkyl;

R_4 is hydrogen, C_1-C_6 alkyl, fluoro, chloro, bromo, iodo, C_1-C_6 alkoxy, amino, NH(C_1-C_6 alkyl), N(C_1-C_6 alkyl) (C_1-C_2 alkyl), SO_n(C_1-C_6 alkyl), wherein n is 0, 1 or 2, cyano, hydroxy, carboxy, or amido, wherein said C_1-C_6 alkyls may be substituted by one to three of hydroxy, amino, carboxy, amido, $NHC(=O)$(C_1-C_4 alkyl), NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), $C(=O)O$(C_1-C_4 alkyl), C_1-C_3 alkoxy, C_1-C_3 thioalkyl, fluoro, bromo, chloro, iodo, cyano or nitro;

R_5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinolyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzoisothiazolyl, thiazolyl, isoxazolyl, benzisoxazolyl, benzimidazolyl, triazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl benzoxazolyl, oxazolyl, pyrrolidinyl, thiazolidinyl, piperazinyl, piperidinyl, tetrazolyl, or 3- to 8-membered cycloalkyl or 9- to 12-membered bicycloalkyl, optionally containing one or two of O, S or N-Z wherein Z is hydrogen, C_1-C_4 alkyl, C_1-C_4 alkanoyl, phenyl or benzyl, wherein each one of the above groups may be substituted independently by from one to three of fluoro, chloro, bromo, formyl, C_1-C_6 alkyl, C_1-C_6 alkoxy or trifluoromethyl, or one of hydroxy, iodo, cyano, nitro, amino, cyclopropyl, NH(C_1-C_4 alkyl), N(C_1-C_4 alkyl)(C_1-C_2 alkyl), COO(C_1-C_4 alkyl), CO(C_1-C_4 alkyl), SO_2NH(C_1-C_4 alkyl), SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl), SO_2NH_2, $NHSO_2$(C_1-C_4 alkyl), S(C_1-C_6 alkyl), SO_2(C_1-C_6 alkyl), wherein said C_1-C_4 alkyl and C_1-C_6

alkyl may have one double or triple bond and may be substituted by one or two of fluoro, chloro, hydroxy, amino, methylamino, dimethylamino or acetyl; with the proviso that R_5 is not unsubstituted phenyl;

R_{11} is hydrogen, hydroxy, fluoro, chloro, $COO(C_1$-C_2 alkyl), cyano, or $CO(C_1$-C_2 aklyl); and

R_{12} is hydrogen or C_1-C_4 alkyl.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 93/11333

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D487/04 A61K31/505 //(C07D487/04,239:00,231:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 287 907 (BOEHRINGER) 26 October 1988 see claims 1,4 & US,A,4 904 666 (BOEHRINGER) 27 February 1990 cited in the application --- -/--	1,11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 March 1994	14.04.94
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Authorized officer Alfaro Faus, I

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INTERNATIONAL SEARCH REPORT

Inter. nal Application No
PCT/US 93/11333

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHEMICAL ABSTRACTS, vol. 108, no. 9, 1988, Columbus, Ohio, US; abstract no. 75765k, A. HASAN ET AL. 'Studies in nucleosides. Part XV. Synthesis of 6-methoxy/methylthio -4-N-substituted-1-(2-tetrahydrofuranyl)1H -pyrazolo[3,4-d]pyrimidines and their biological activity' page 722 ; see abstract and 12th collective index, page 78646, column 2, lines 35,36,38,76,77,79; column 3, lines 33-35,37-39,41,57,58,60,115,116,118 & INDIAN J. CHEM., SECT. B 1987, 26B(3), 284-6 ---	1,11
X	CHEMICAL ABSTRACTS, vol. 109, no. 9, 1988, Columbus, Ohio, US; abstract no. 73841d, K. DEO ET AL. 'Nucleosides. Part XVIII. Synthesis of 6-methoxy/methylthio-4-N-subs tituted-1-(2'-tetrahydropyranyl/2'-hydroxy ethoxymethyl-1H-pyrazolo[3,4-d]pyrimidines and their biological activity' page 734 ; see abstract and 12th collective index, page 78646, column 2, lines 80,81,83; column 3, lines 62,63,65,118,119; page 78674, column 1, lines 2,3 & INDIAN J. CHEM., SECT. B 1987, 26B (10), 963 - 7 ---	1,11
X	JOURNAL OF ORGANIC CHEMISTRY vol. 23 , 1958 , EASTON US pages 191 - 200 C.C. CHENG ET AL. 'Potential purine antagonists. VII. Synthesis of 6-alkylpyrazolo[3,4-d]pyrimidines' see tables II and III ---	1
X	JOURNAL OF ORGANIC CHEMISTRY vol. 21 , 1956 , EASTON US pages 1240 - 1256 C.C. CHENG ET AL. 'Potential purine antagonists. Vi. Synthesis of 1-alkyl- and 1-aryl-4-substituted pyrazolo[3,4-d]pyrimidines' see tables --- -/--	1

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 93/11333

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JOURNAL OF MEDICINAL AND PHARMACEUTICAL CHEMISTRY vol. 5, no. 1 , 1962 , EASTON US pages 588 - 607 E.Y. SUTCLIFFE ET AL. 'Potential purine antagonists. XXXII. The synthesis and antitumor activity of certain compounds related to 4-aminopyrazolo[3,4-d]pyrimidine' see tables	1
X	CHEMICAL ABSTRACTS, vol. 111, no. 3, 1989, Columbus, Ohio, US; abstract no. 19378m, T. POLI ET AL. 'Synthesis and in-vitro antifugal activity of 6-trifluoromethylpyrazolo[3,4-d]pyrimidines' page 233 ; see abstract and 12th collective index, page 78637, column 1, lines 30 - 35; page 78638, column 1, lines 40 - 46 & PESTIC. SCI. 1989, 25(2), 161-9	1
X	JOURNAL OF HETEROCYCLIC CHEMISTRY vol. 19 , 1982 , PROVO US pages 1565 - 1567 K. SENGA ET AL. 'Synthesis and xanthine oxidase inhibitory activity of 4,6-disubstituted 1-p-chlorophenylpyrazolo[3,4-d]pyrimidines' see compuonds 5,8 and 9	1
X	US,A,4 139 705 (J.E. DUNBAR ET AL.) 13 February 1979 see claim 1	1
X	DE,A,24 30 454 (K. THOMAE) 15 January 1976 see example 27, lines 1,2 and example 31, lines 1,2	1
X	US,A,3 551 428 (J. DRUEY ET AL.) 20 December 1970 see claim 1	1
X	FR,A,1 311 787 (CIBA) 5 November 1962 see page 7, column 1, line 1 - line 12	1
X	FR,A,2 073 274 (SAPCHIM-FOURNIER-CIMAG) 1 October 1971 see page 1, line 1 - line 14	1

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INTERNATIONAL SEARCH REPORT

Inter al Application No
PCT/US 93/11333

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 063 245 (M. A. ABREU ET AL.) 5 November 1991 cited in the application see claim 1 -----	1,11

1

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 93/ 11333

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 12 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. aal Application No
PCT/US 93/11333

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		AU-B-	613907	15-08-91
		AU-A-	1450688	20-10-88
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		ZA-A-	8802618	17-10-88
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		JP-A-	63258880	26-10-88
		SU-A-	1701111	23-12-91
		ZA-A-	8802618	17-10-88
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DE-A-2430454	15-01-76	NONE		
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FR-A-1311787		NONE		
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		DE-A,B,C	2061430	24-06-71
US-A-5063245	05-11-91	NONE		